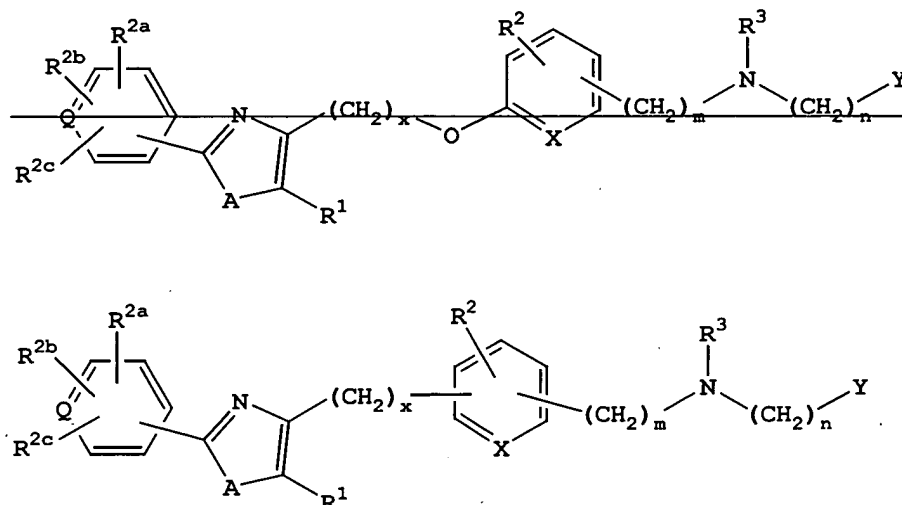


AMENDMENTS TO CLAIMS

Claim 1. (Cancelled).

Claim 2. (Currently Amended) The method as defined in Claim 34 wherein the [[A]] compound having employed has the structure



Claims 3 to 4. (Cancelled).

Claim 5. (Currently Amended) The compound method as defined in Claim 4 34 wherein the compound employed wherein (CH₂)_x is alkylene, alkenylene, allenyl, or alkynylene.

Claims 6 to 9. (Cancelled).

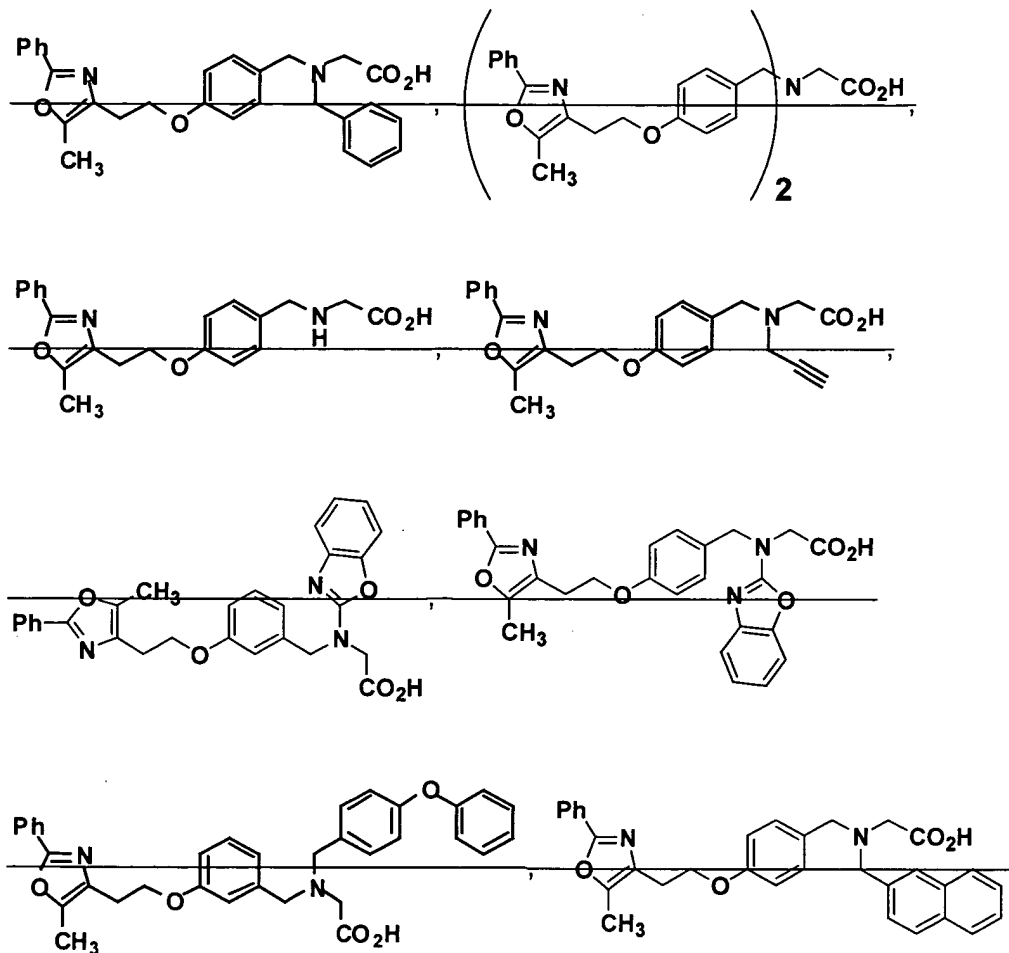
Claim 10. (Currently Amended) The compound method as defined in Claim 4 34 wherein R^{2a} is alkoxy or H, where in the compound employed

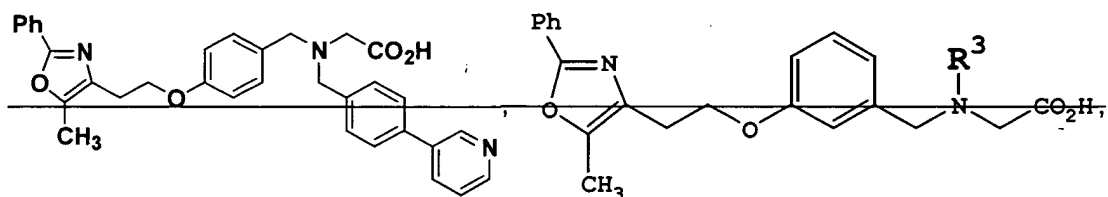
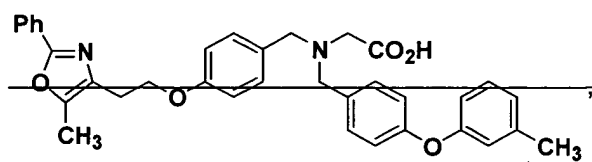
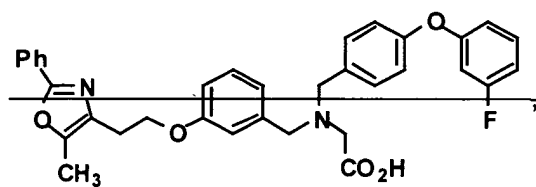
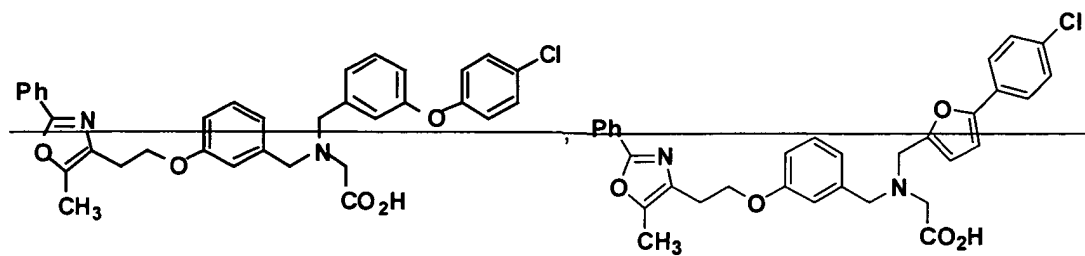
(CH₂)_x is CH₂, (CH₂)₂, (CH₂)₃, or $\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C} \end{array}$, (CH₂)_m is CH₂, or $\begin{array}{c} \text{R}_a \\ | \\ \text{CH} \end{array}$ (where R_a is alkyl or alkenyl), (CH₂)_n is CH₂, R¹ is lower alkyl, preferably —CH₃, R² is H, R^{2a} is H, R⁴ is H, X is CH, and R³ is arylalkyloxycarbonyl, arylheteroarylalkyl, aryloxyarylalkyl, arylalkyl, aryloxycarbonyl, haloaryl-oxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, aryloxyarylalkyl, arylalkenyloxycarbonyl,

cycloalkylaryloxy carbonyl, arylalkylaryloxy carbonyl, heteroaryl-heteroarylalkyl, cycloalkyloxyaryloxy carbonyl, heteroaryl-heteroarylalkyl, alkyloxyaryloxy carbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, alkoxyaryloxy carbonyl, arylthiocarbonyl, cycloheteroalkylalkyloxy carbonyl, cycloheteroalkyloxy carbonyl, or polyhaloalkylaryloxy carbonyl, which may be optionally substituted.

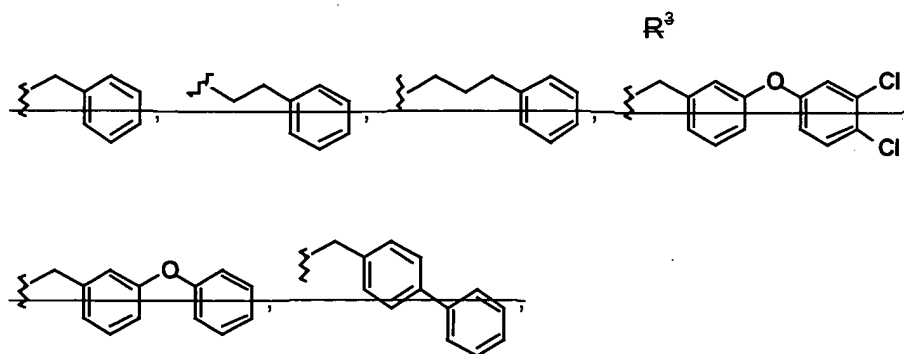
Claims 11 to 15. (Cancelled).

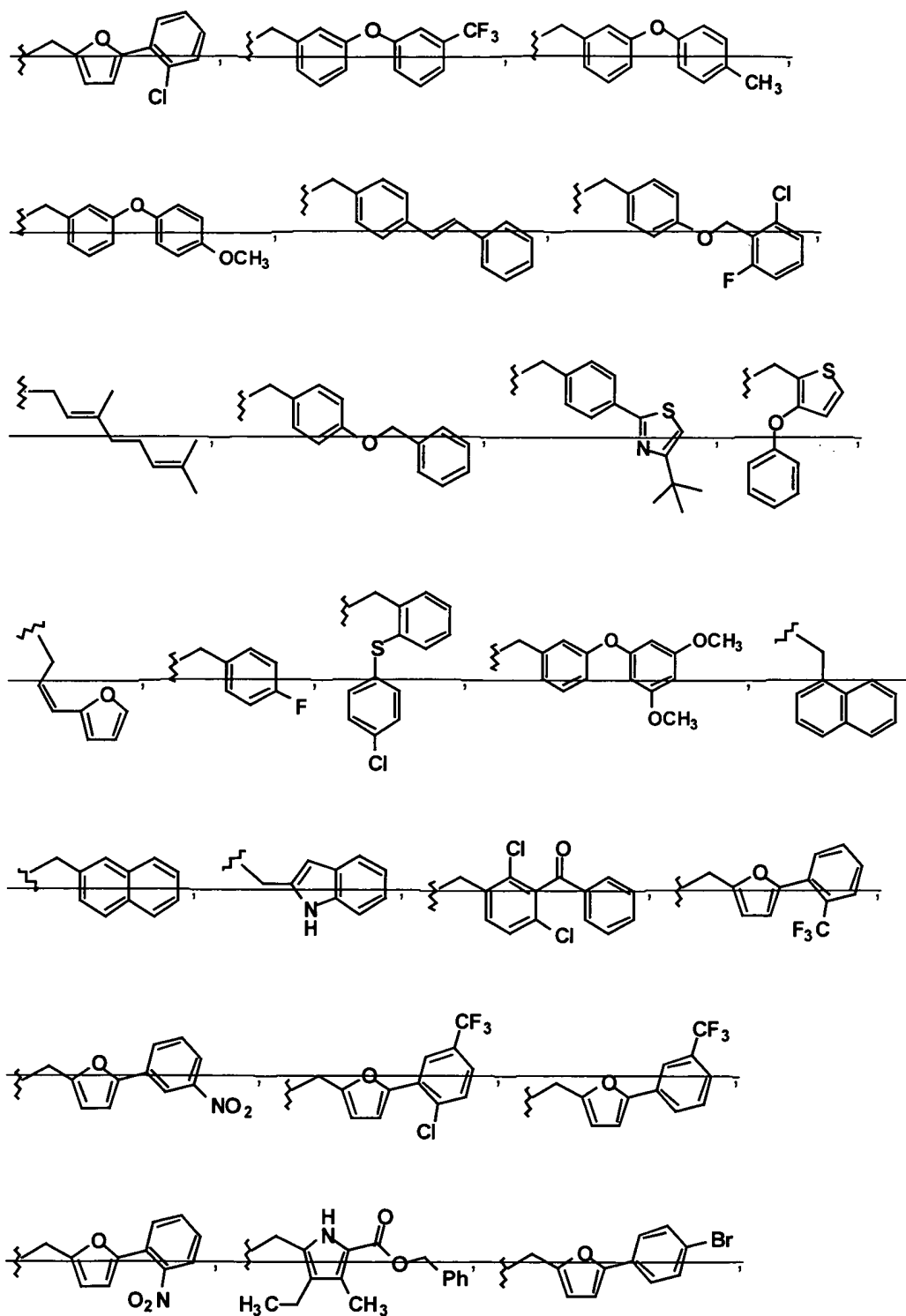
Claim 16. (Currently Amended) The compound method as defined in Claim 1 ~~having~~ 34 wherein the compound employed has the structure

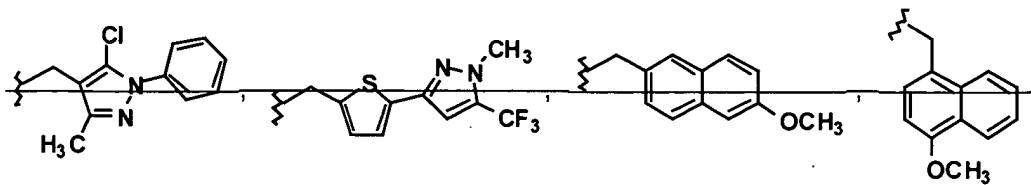
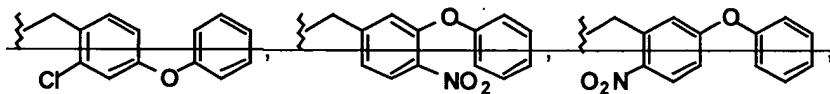
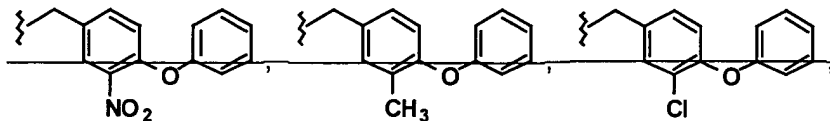
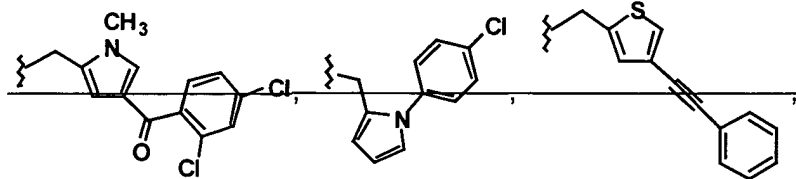
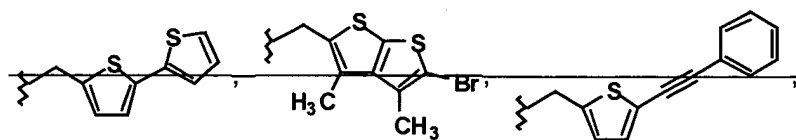
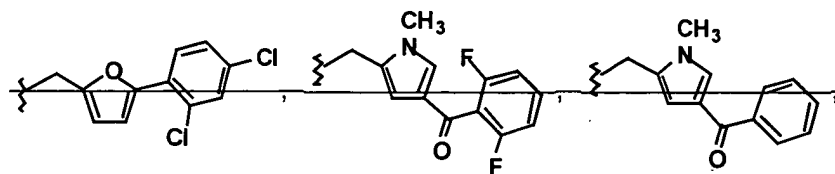
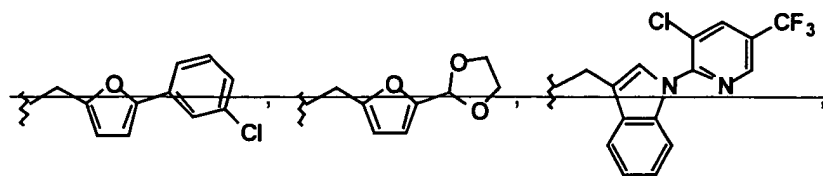


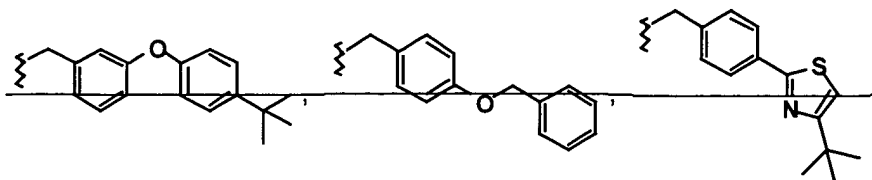
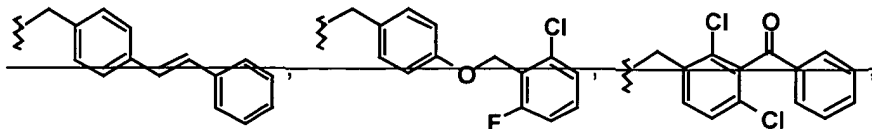
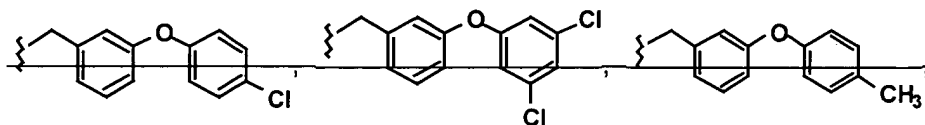
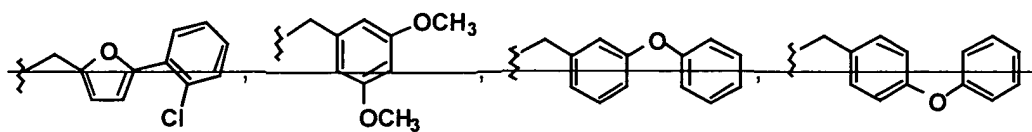
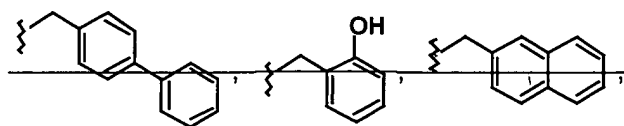
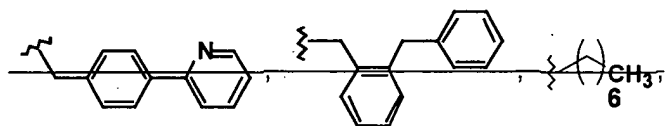
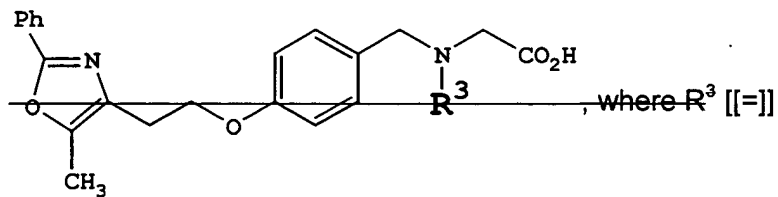
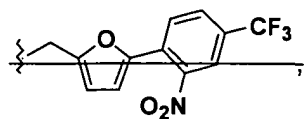


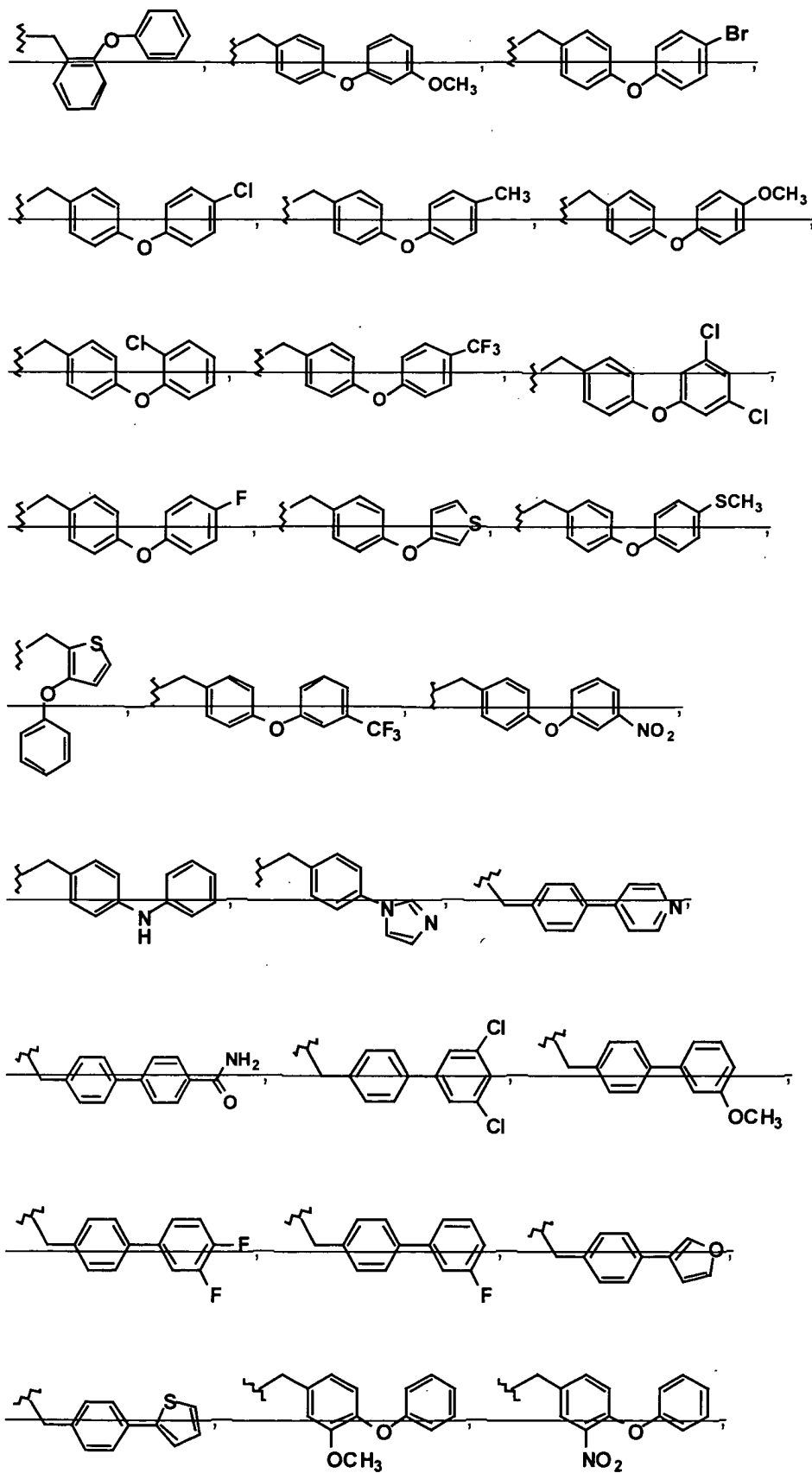
where R^3 [[=]]

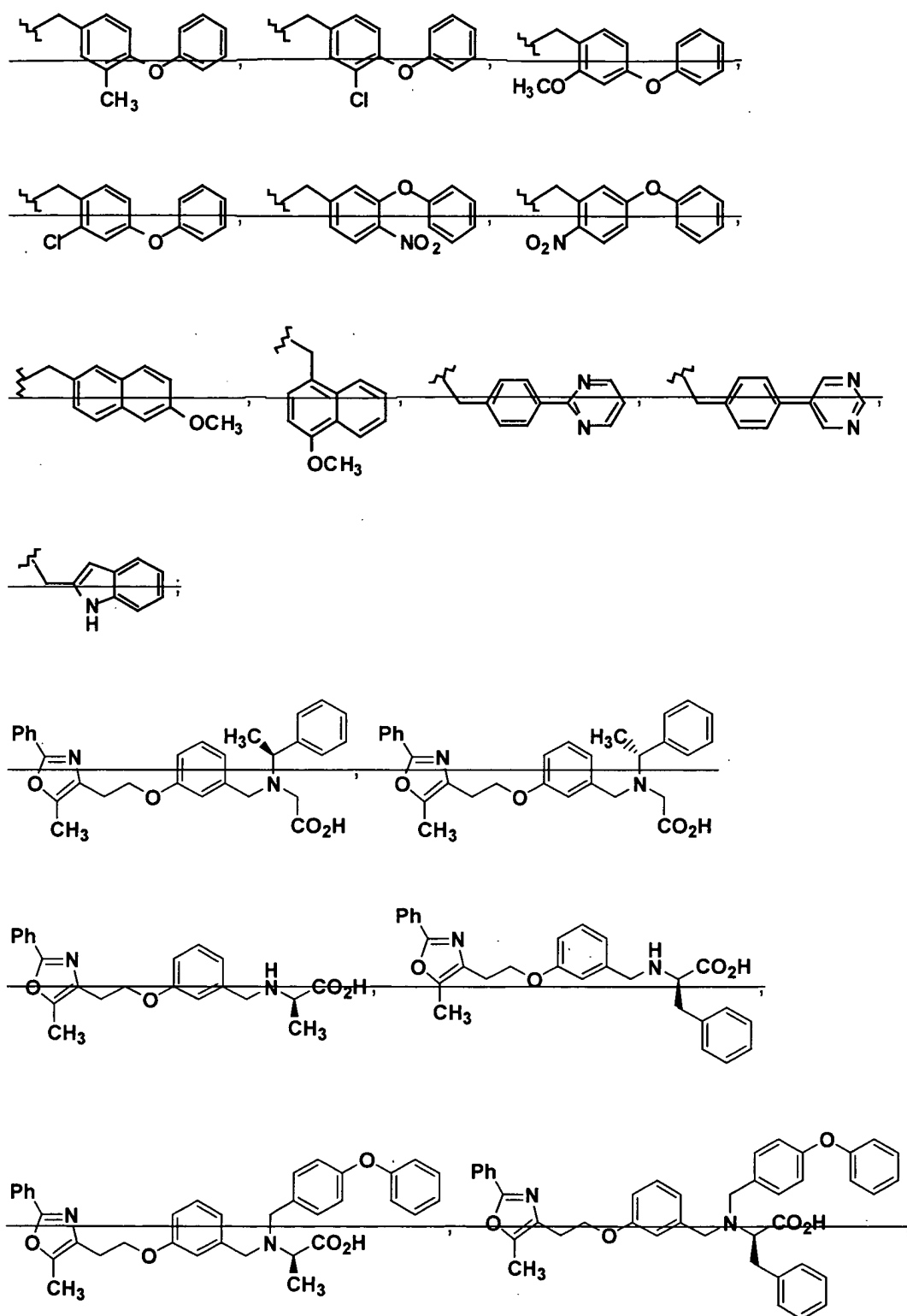


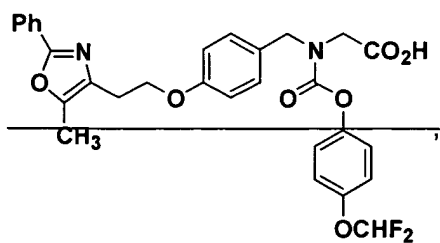
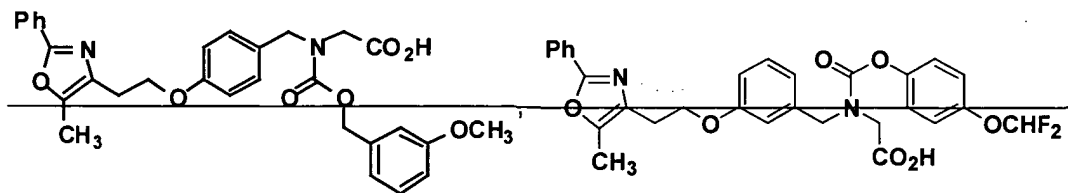
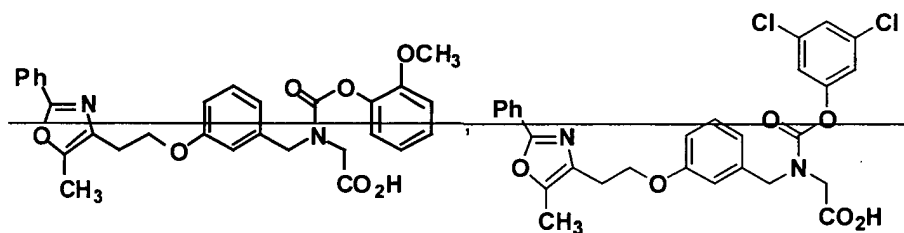
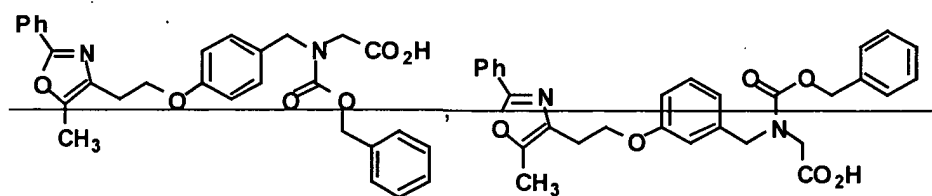
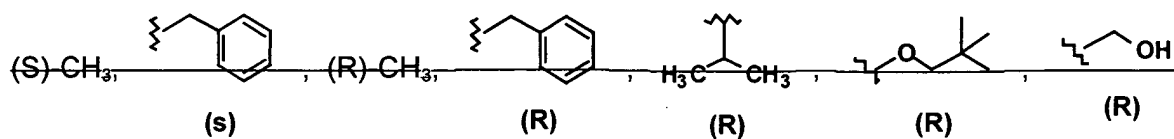
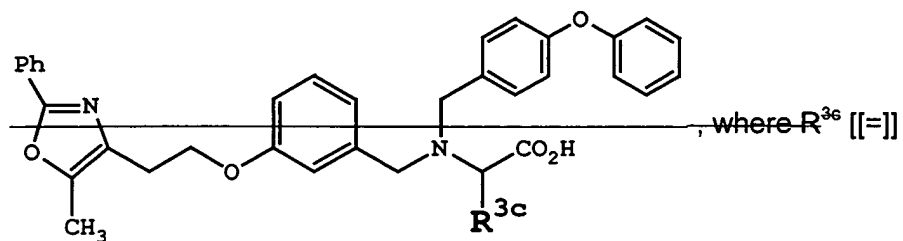


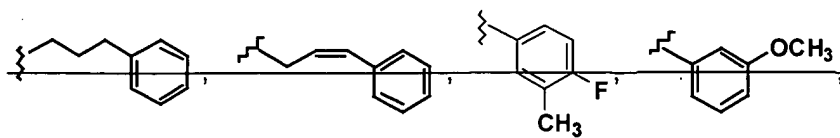
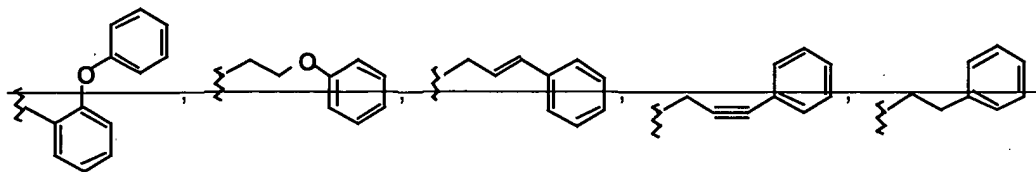
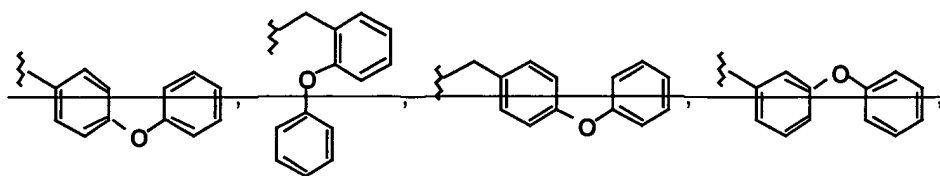
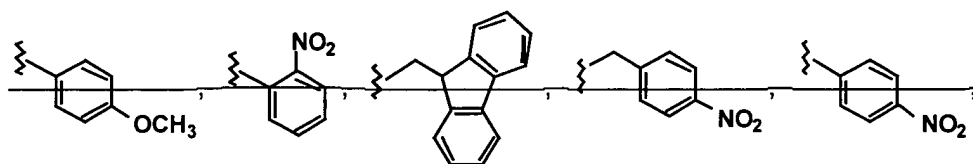
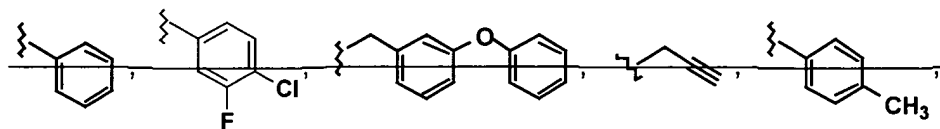
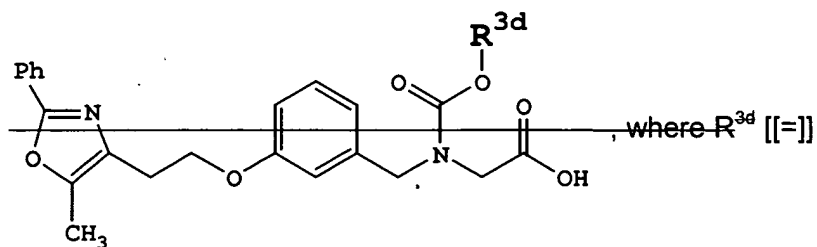
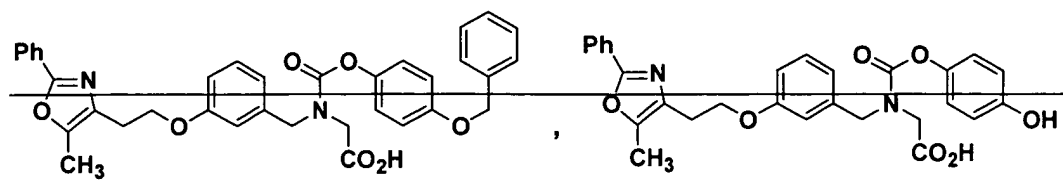


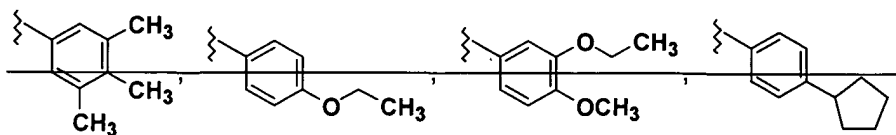
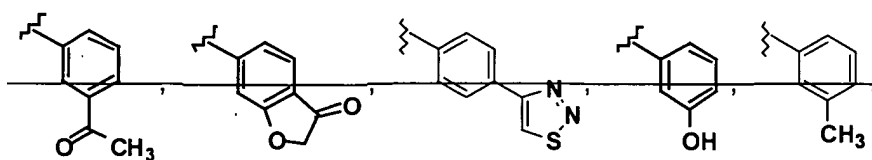
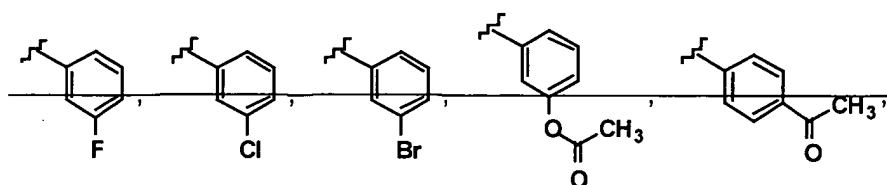
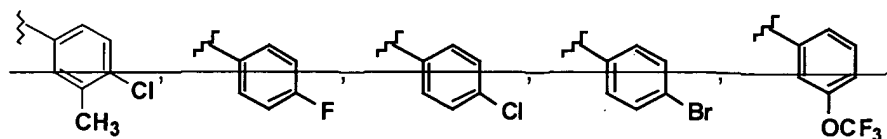
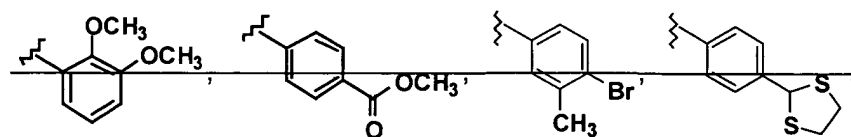
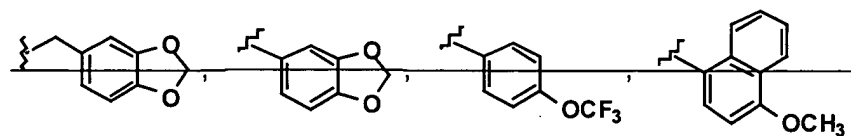
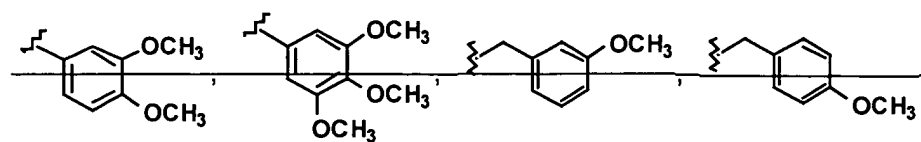


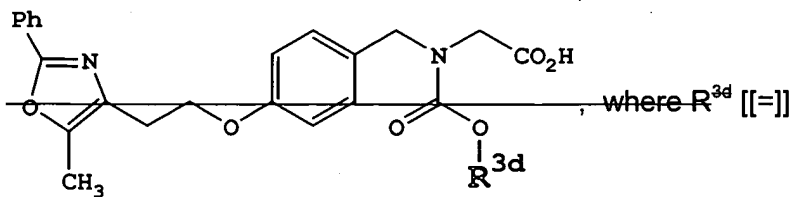
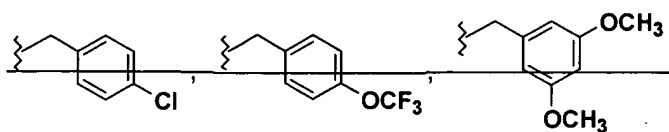
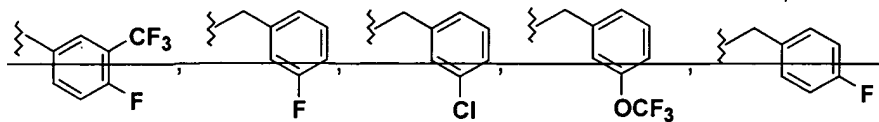
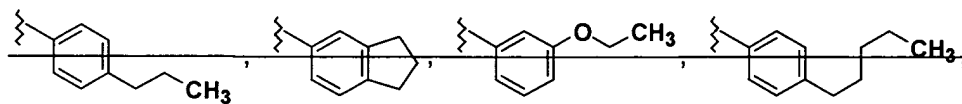
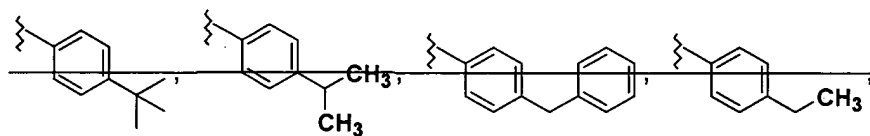
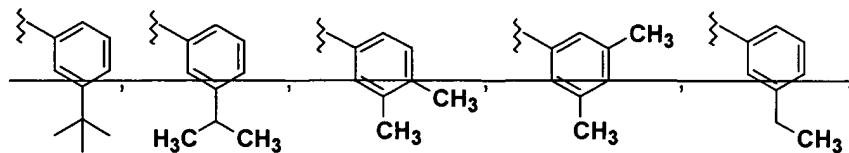
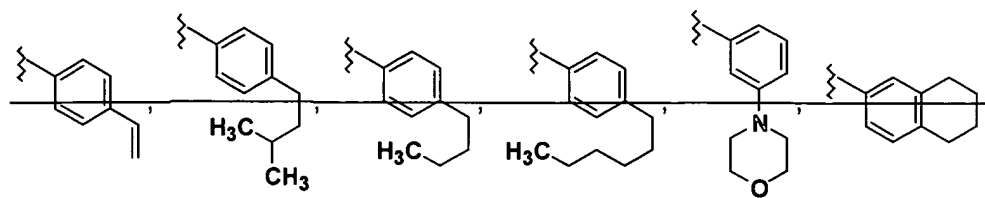


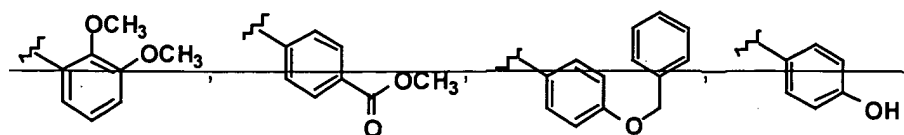
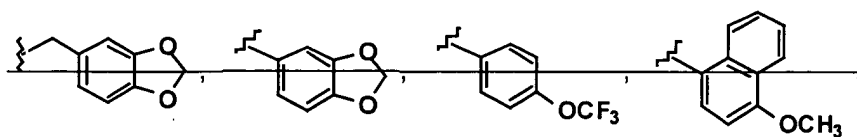
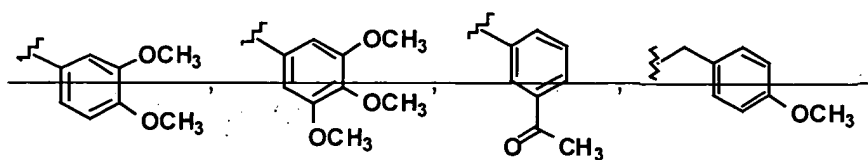
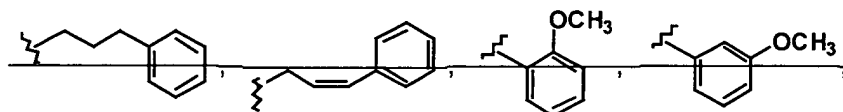
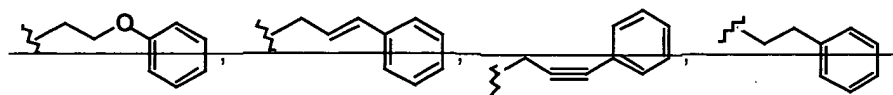
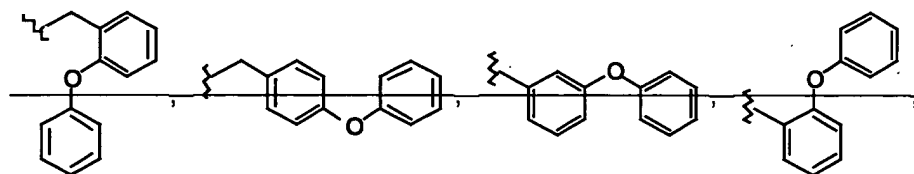
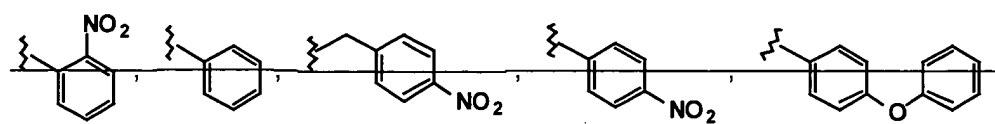
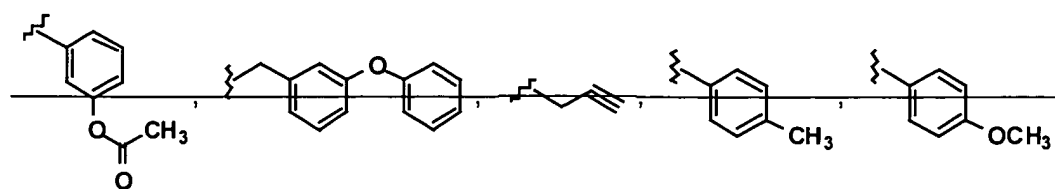


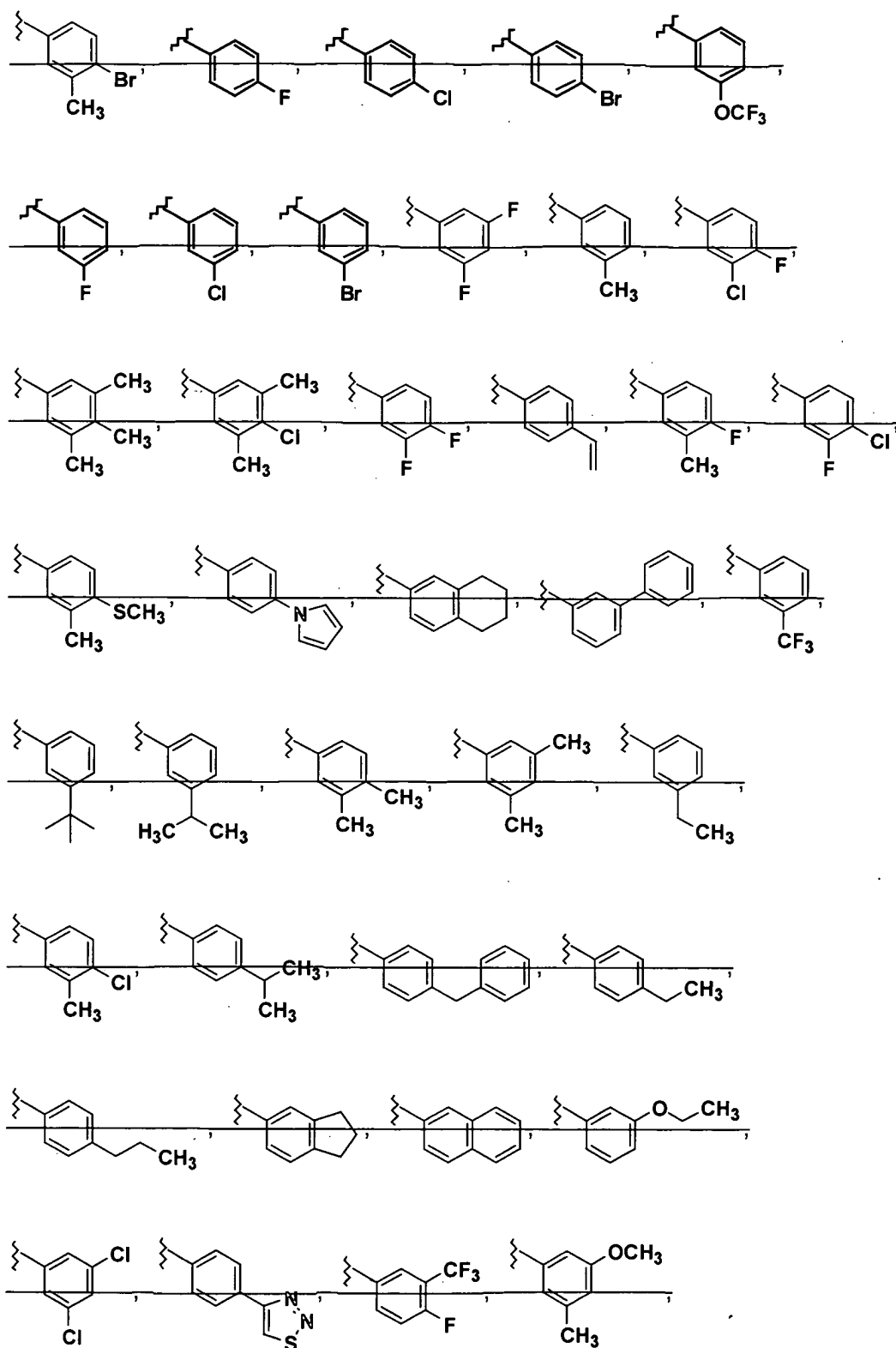


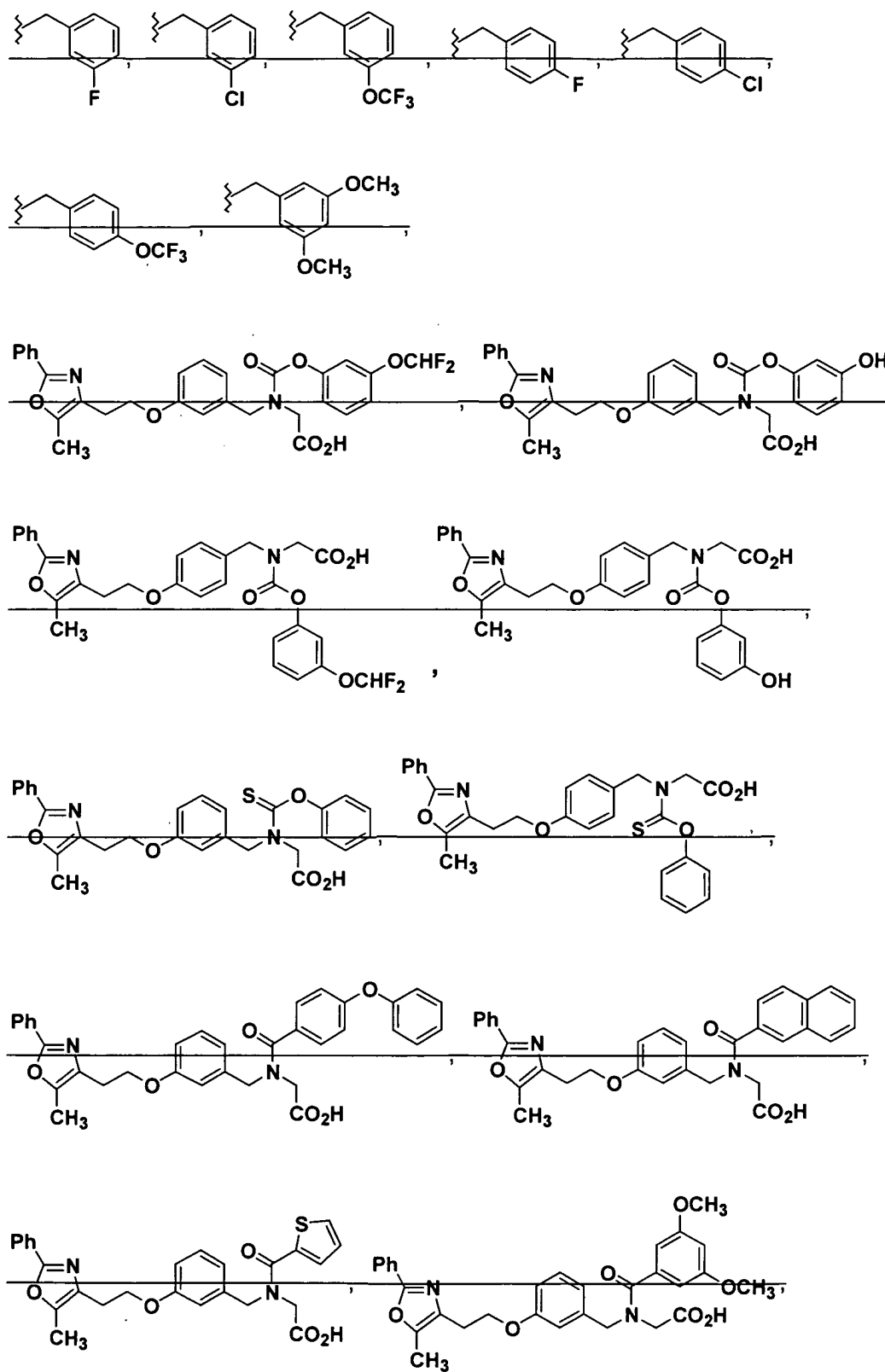


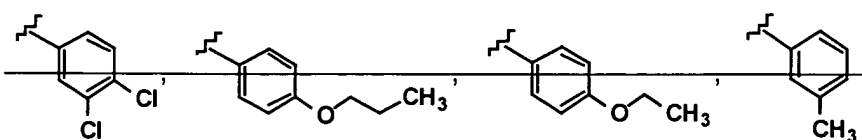
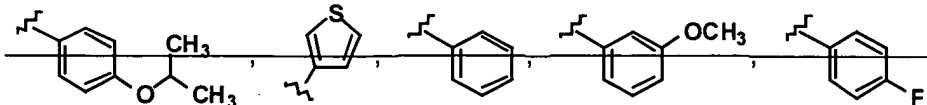
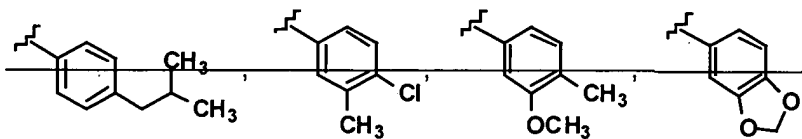
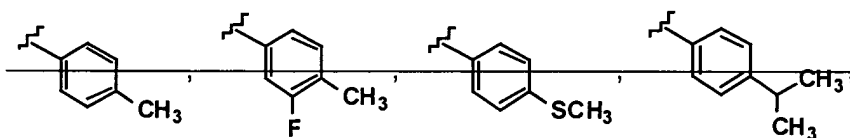
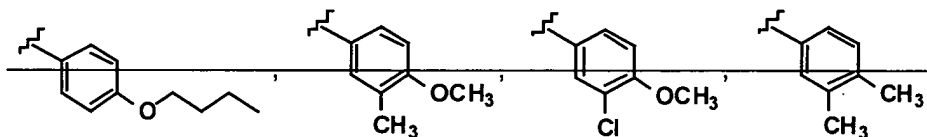
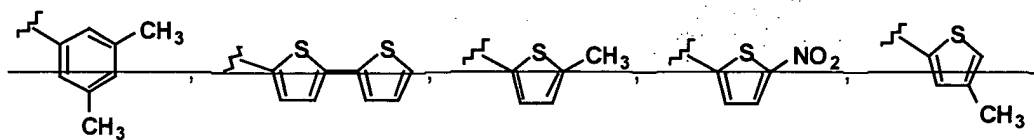
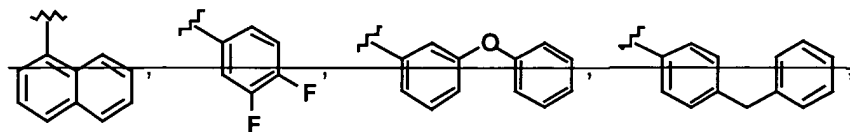
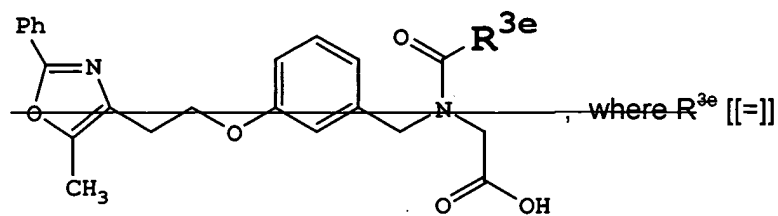


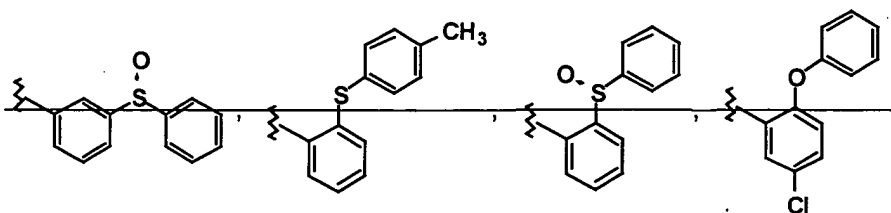
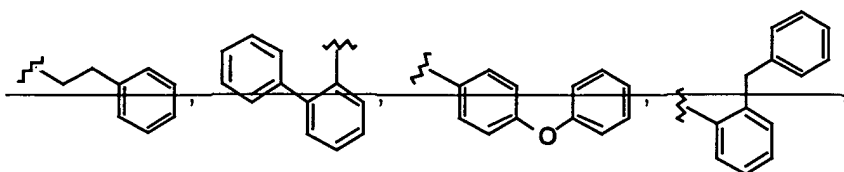
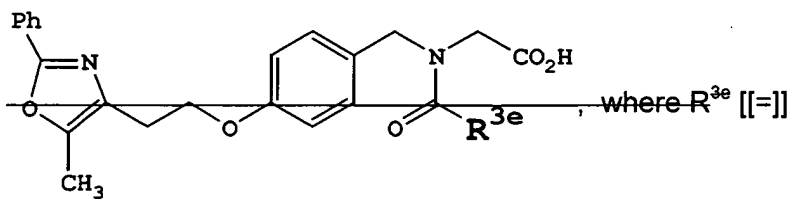
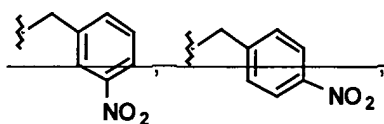
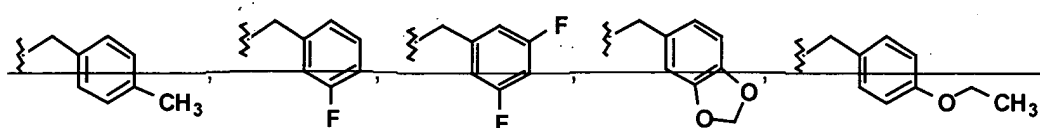
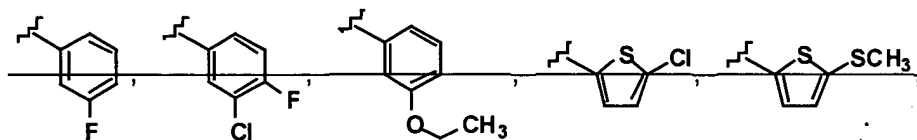
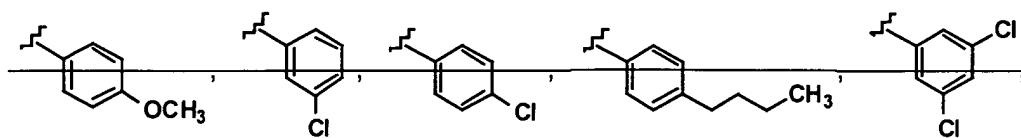


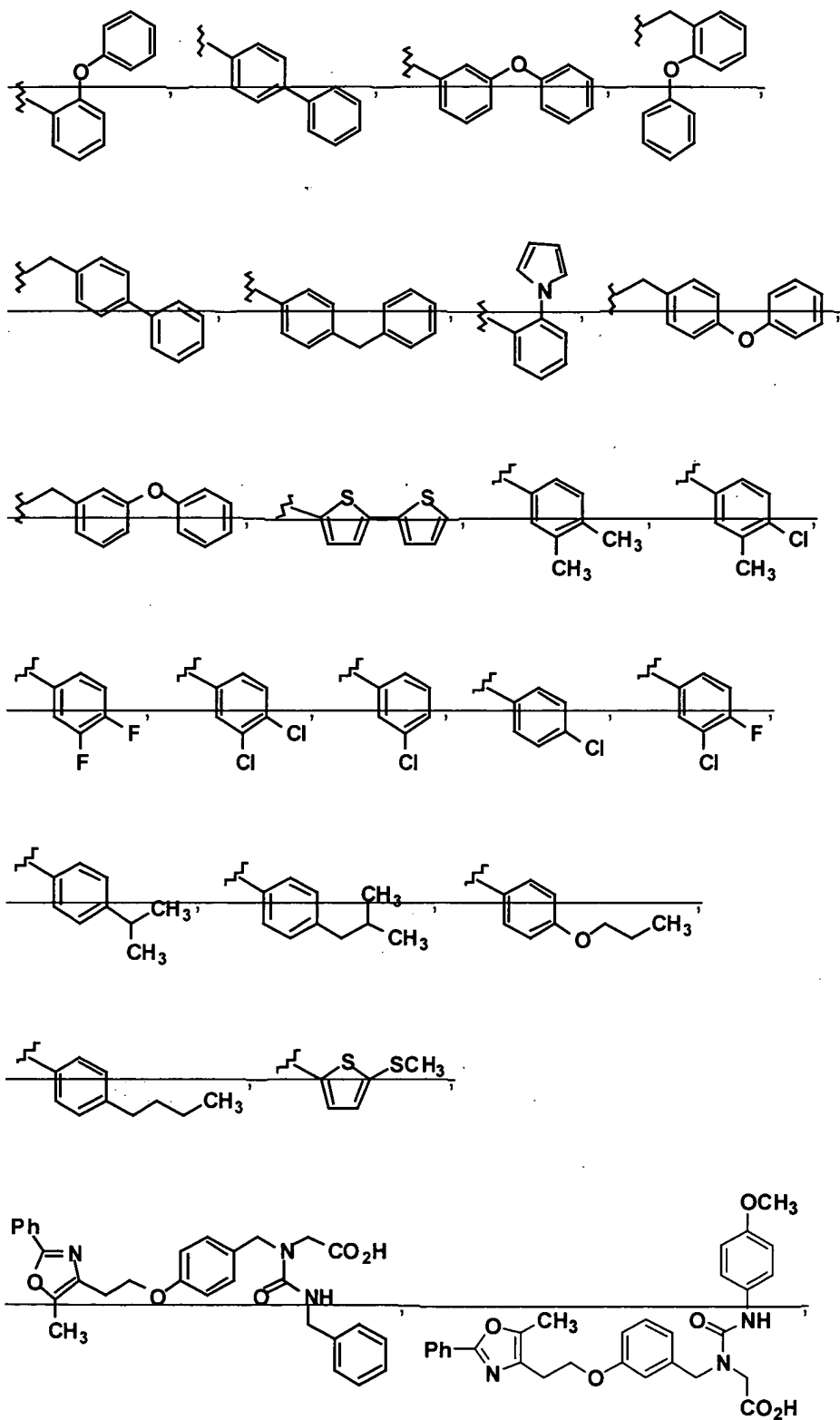


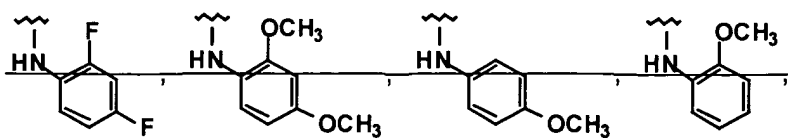
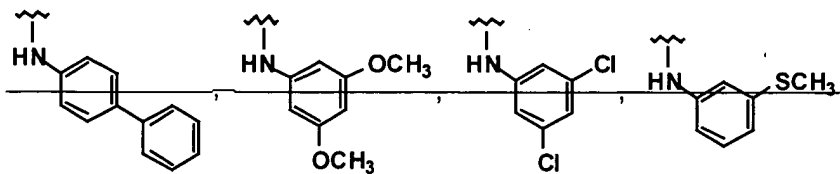
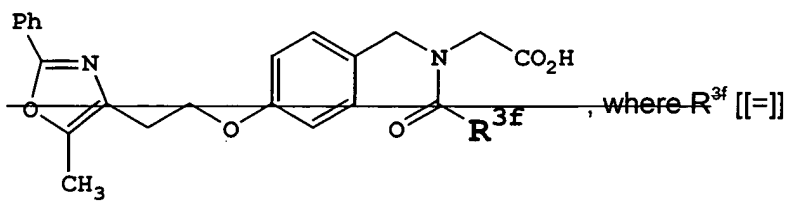
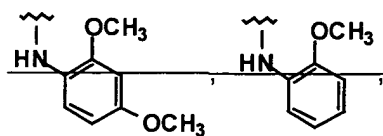
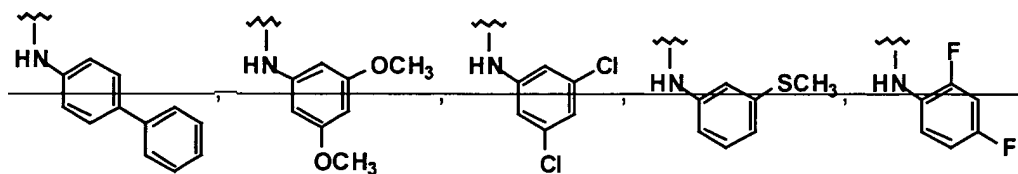
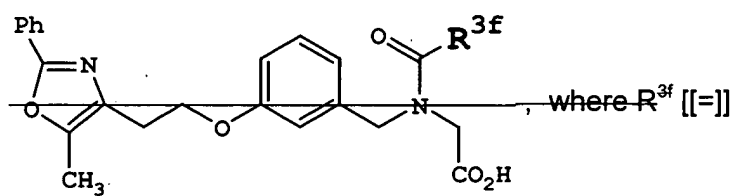
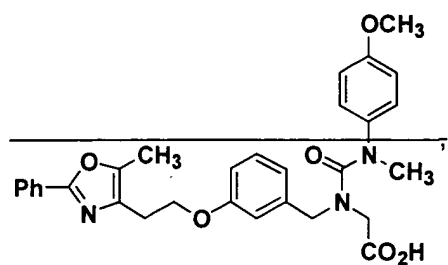


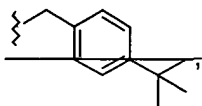
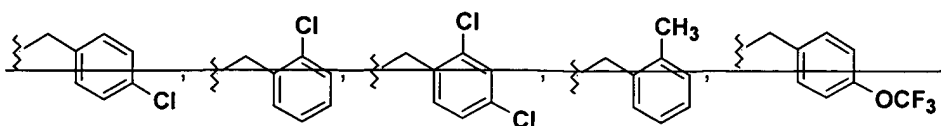
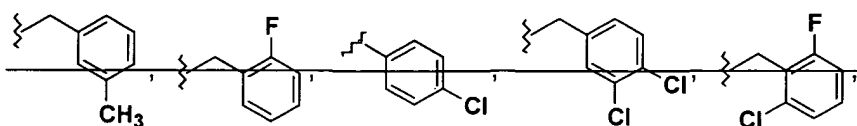
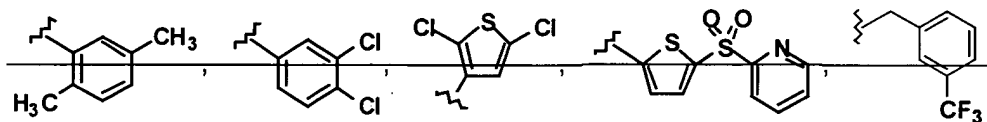
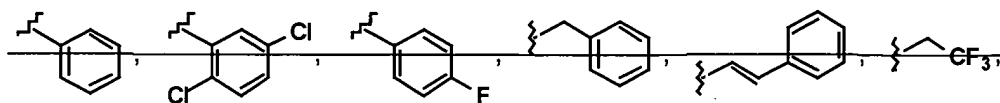
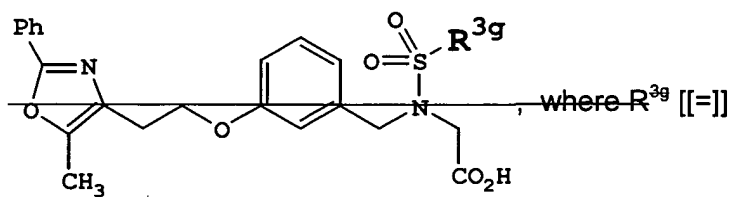
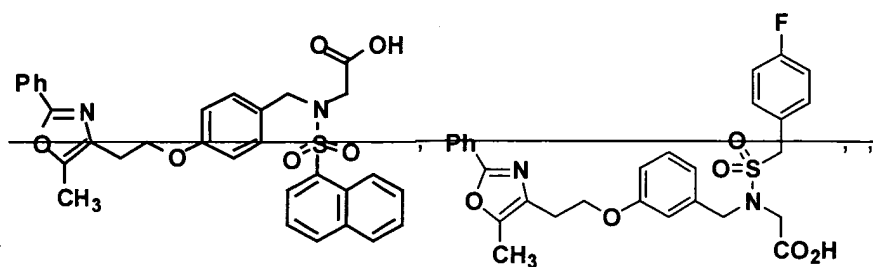


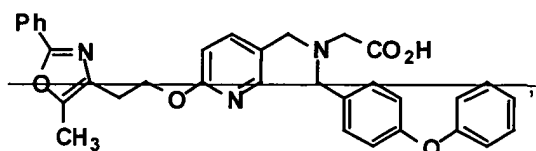
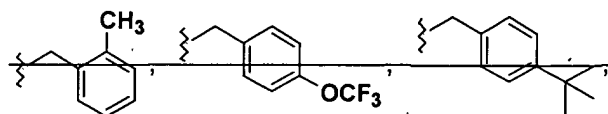
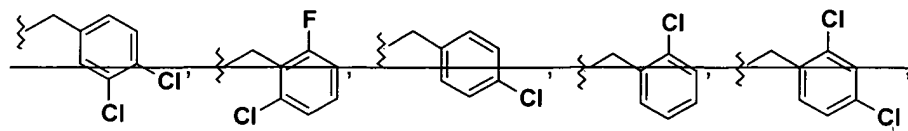
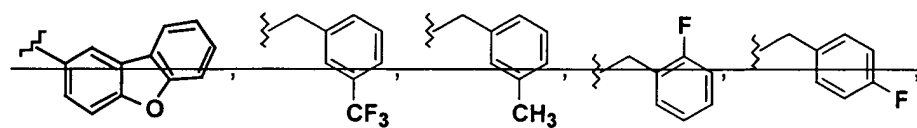
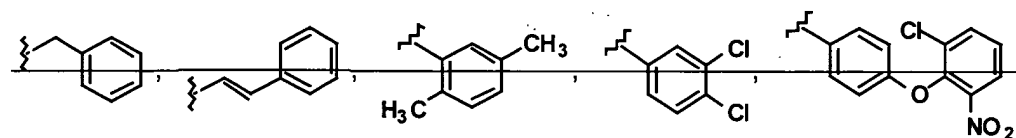
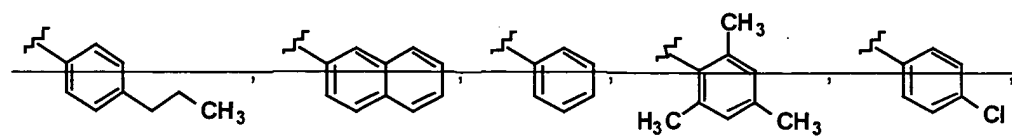
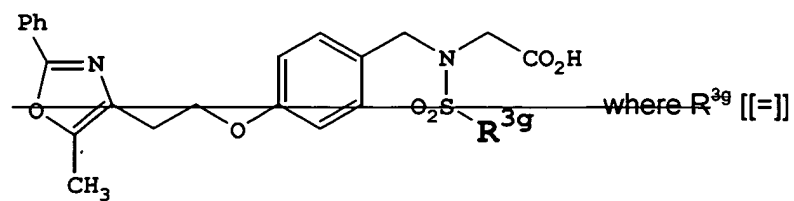


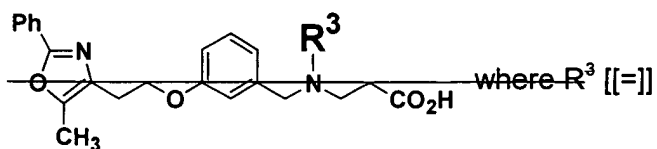
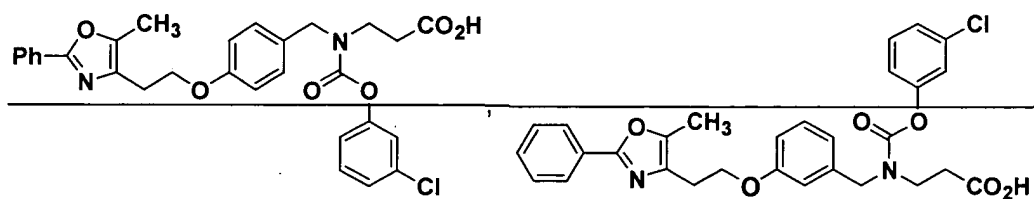
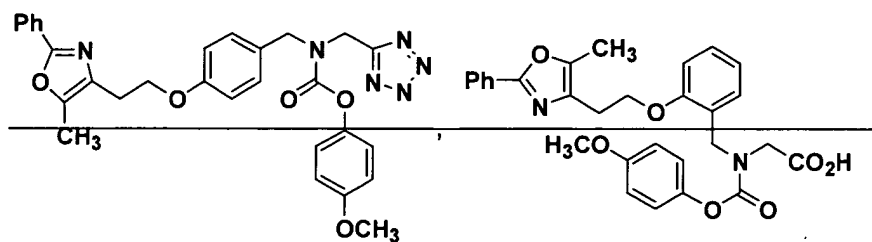
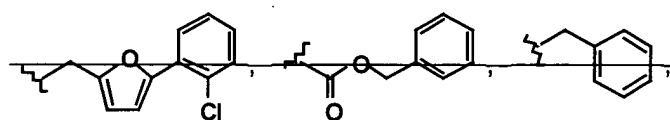
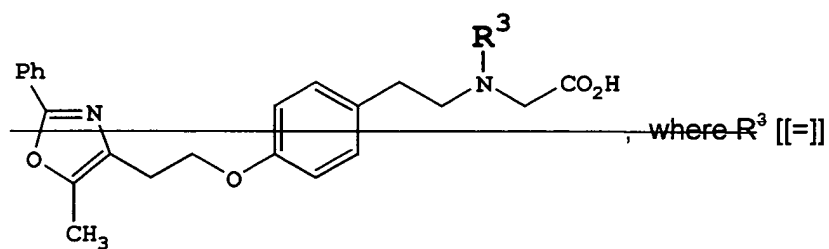
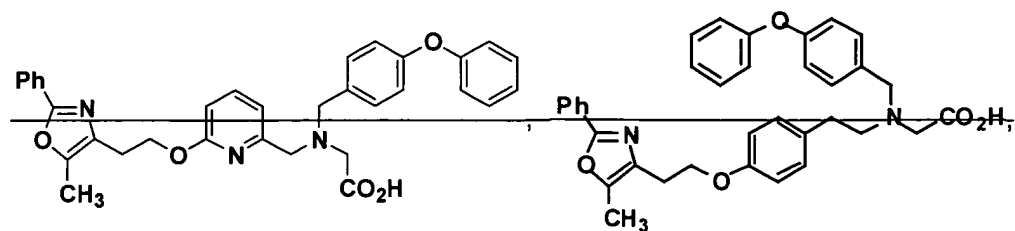


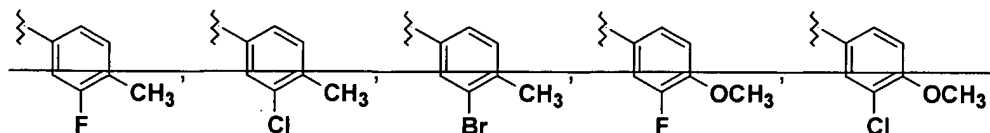
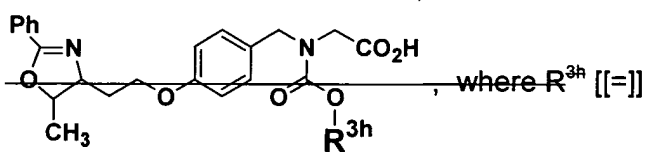
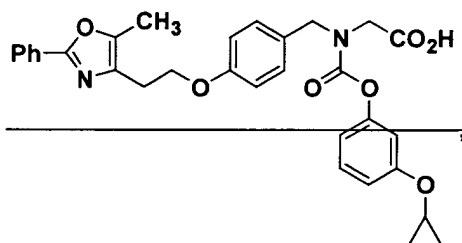
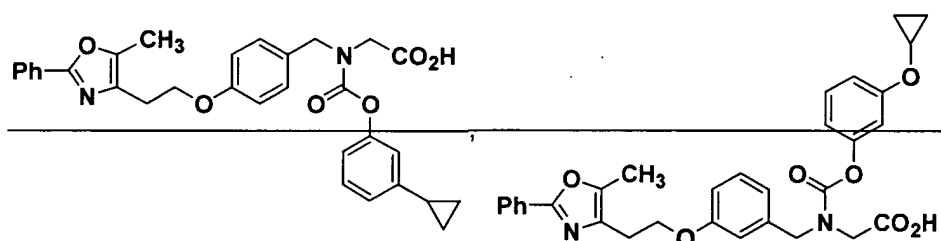
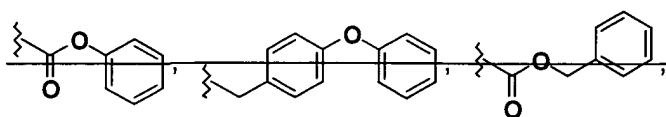
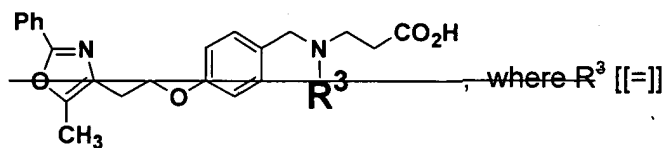
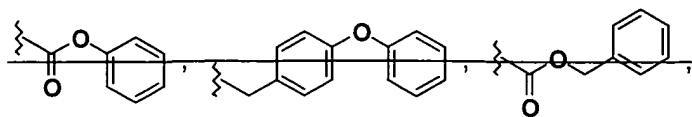


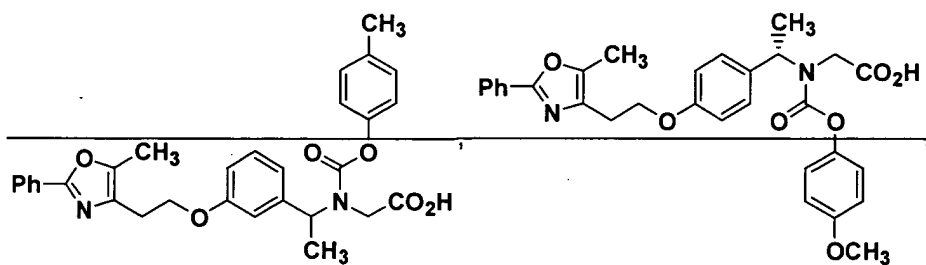
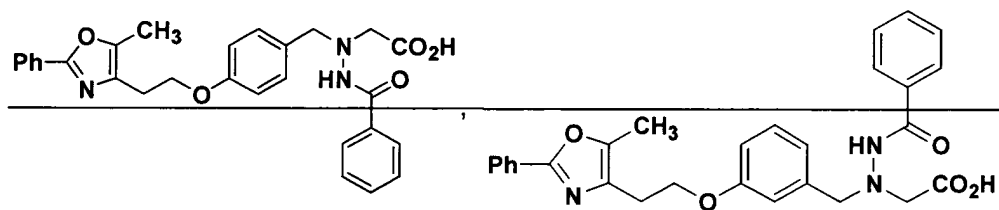
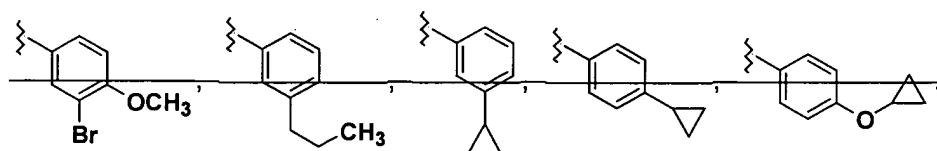
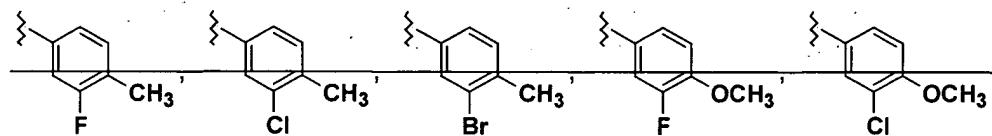
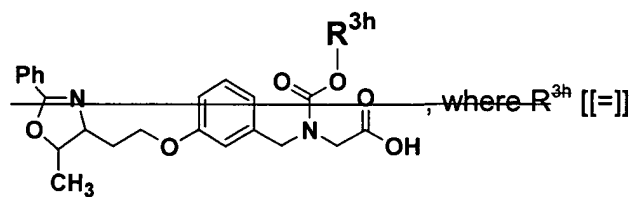
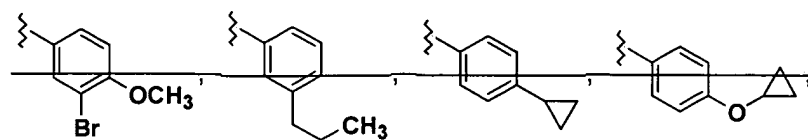


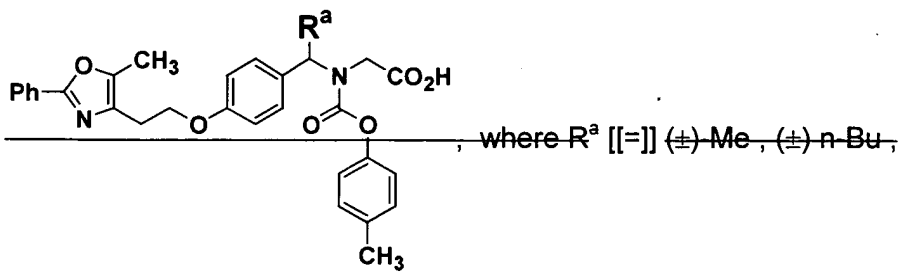
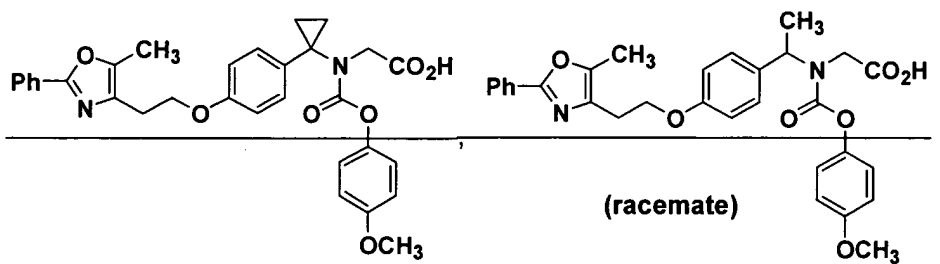
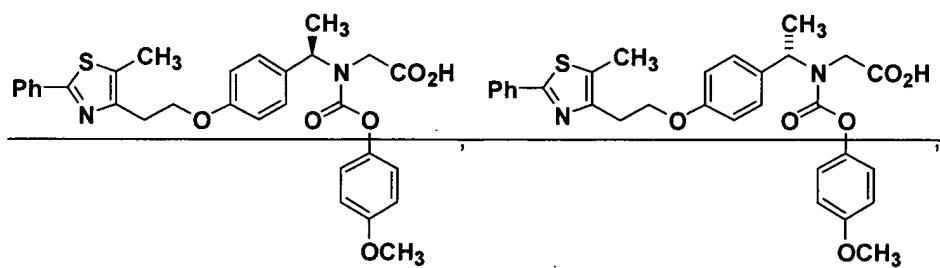
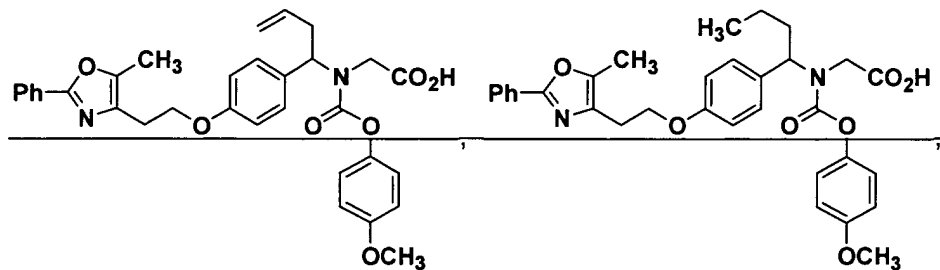
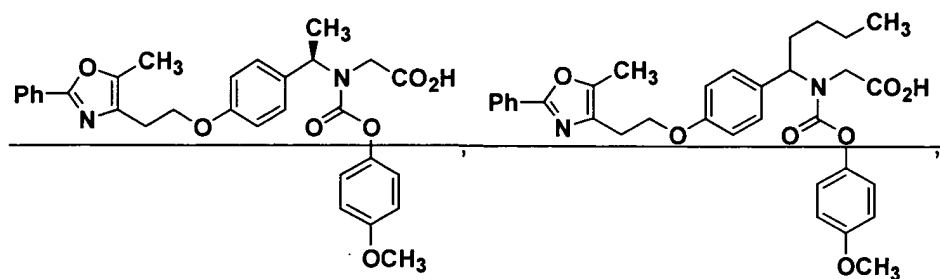


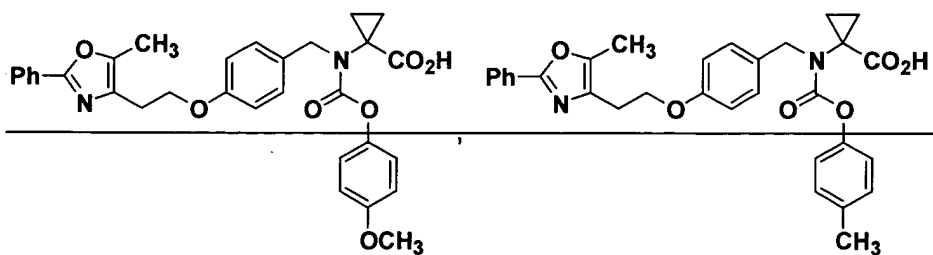
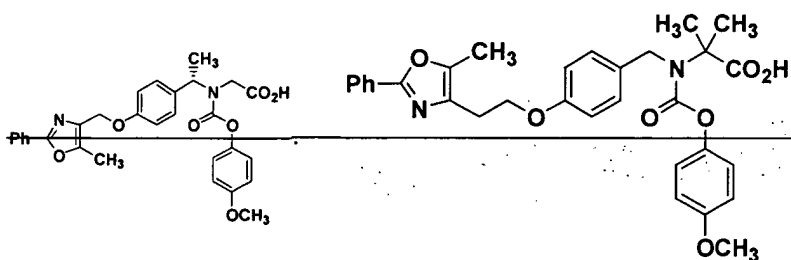
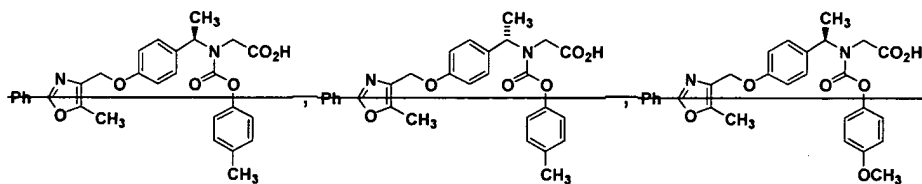
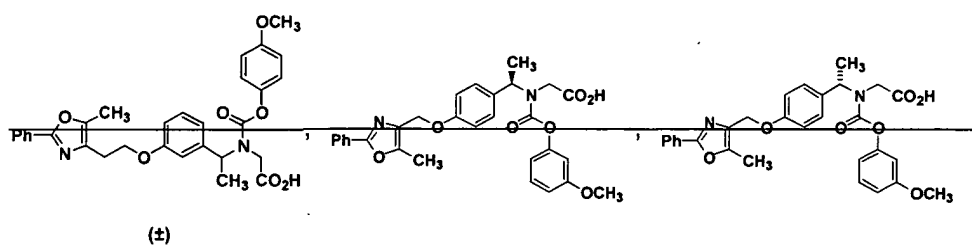
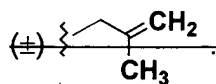
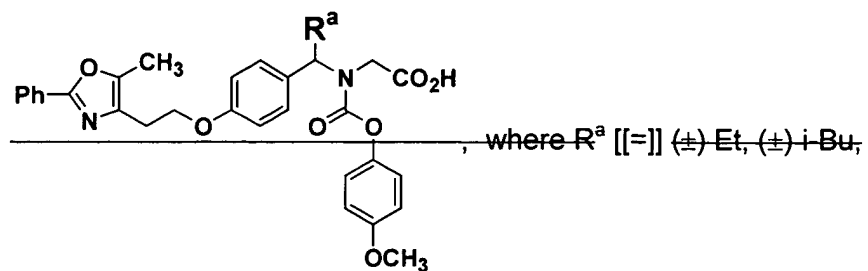


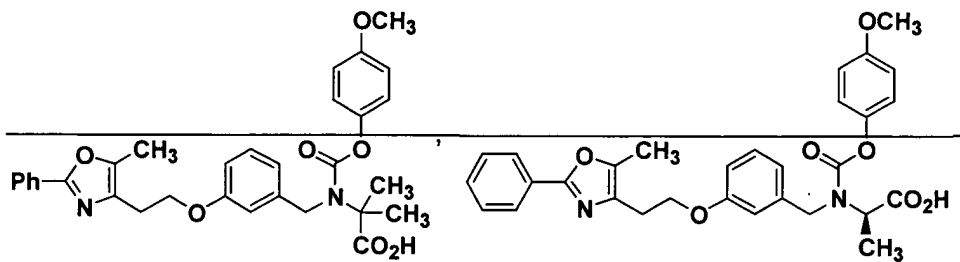
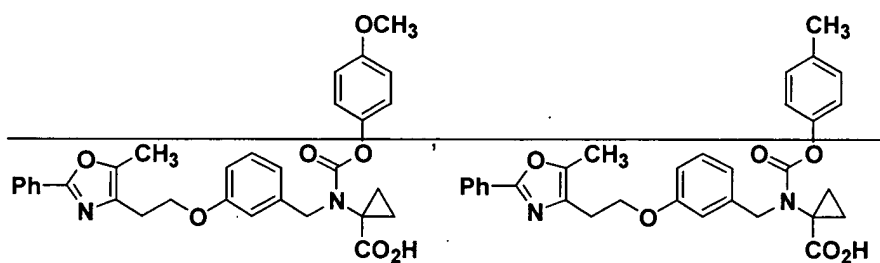
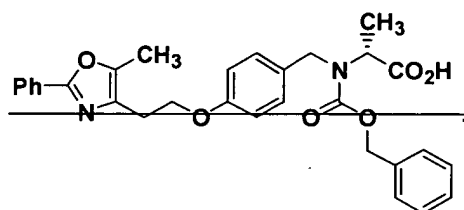
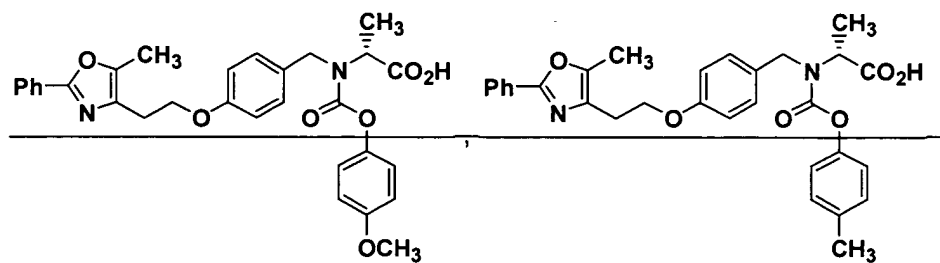
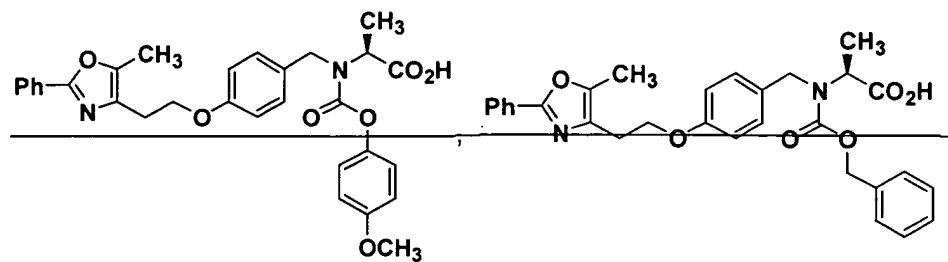


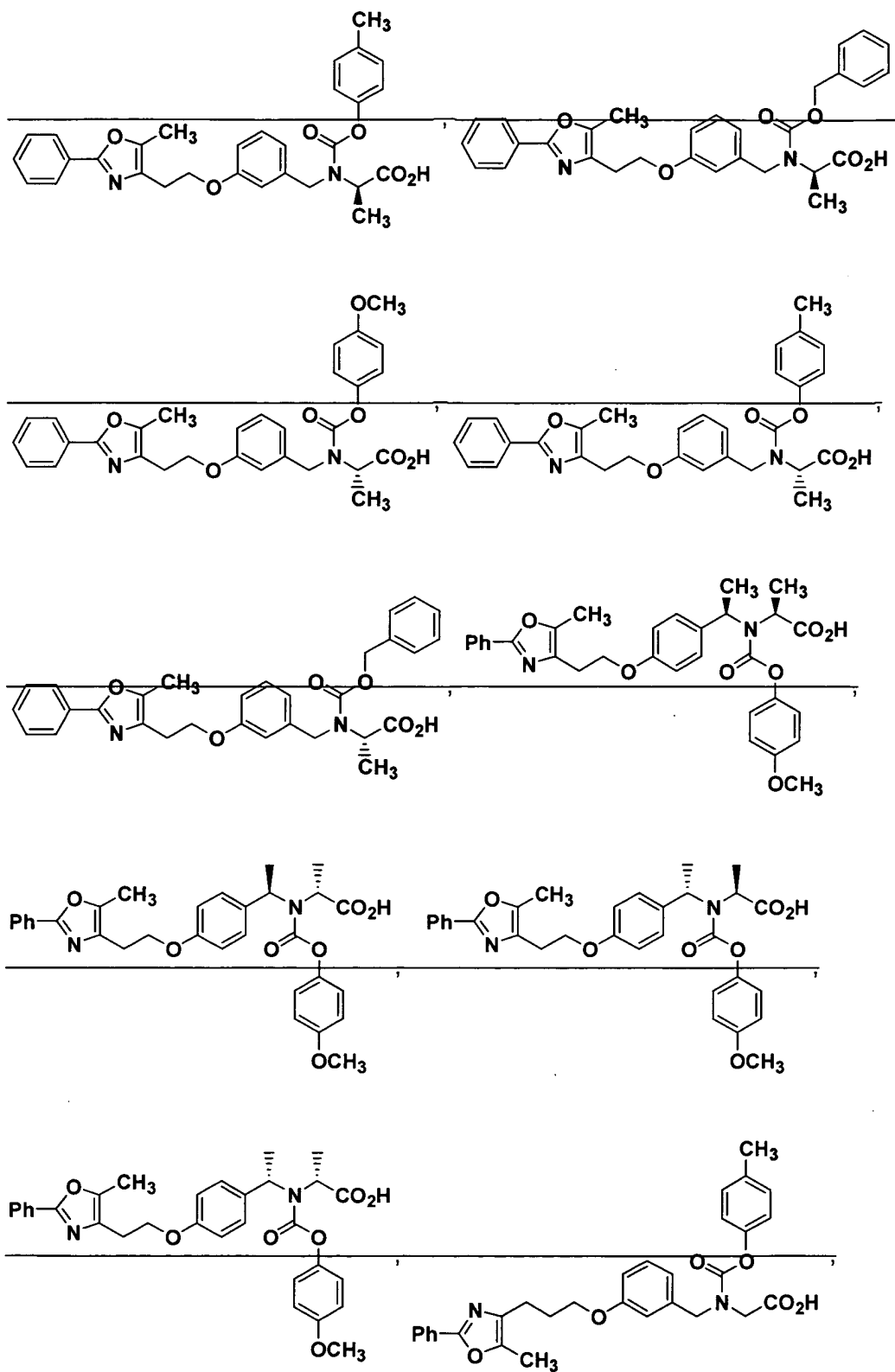


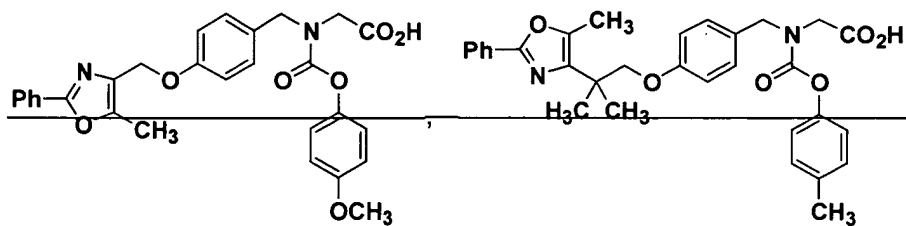
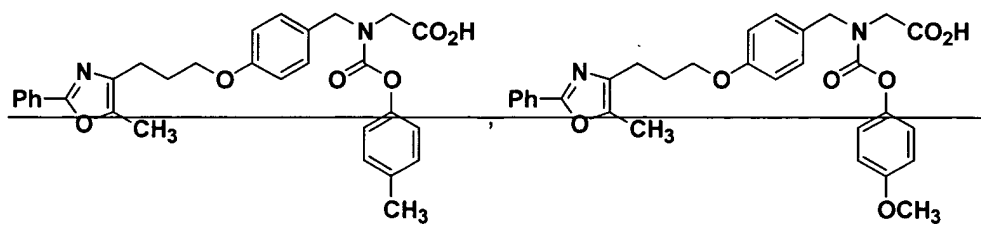
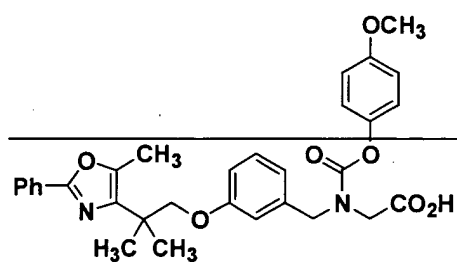
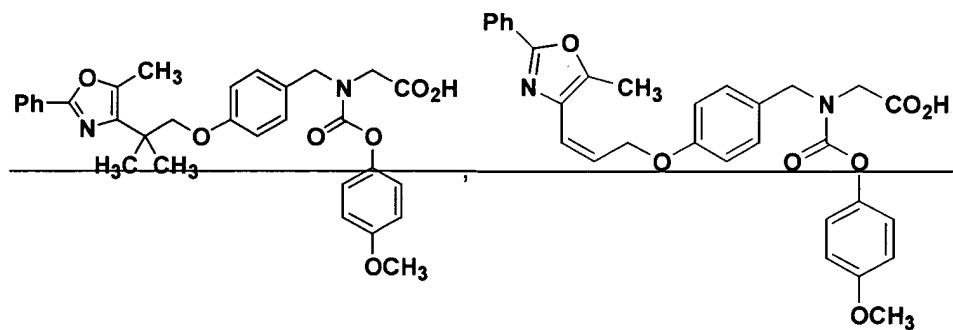
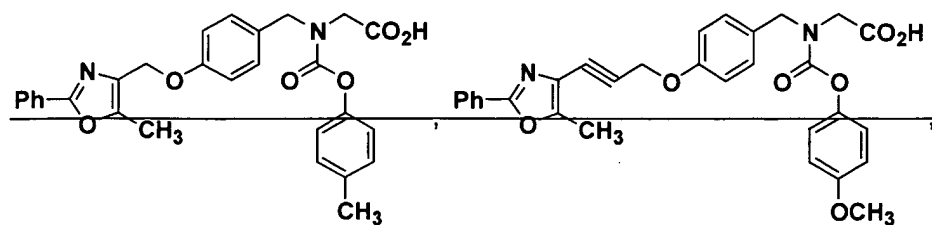


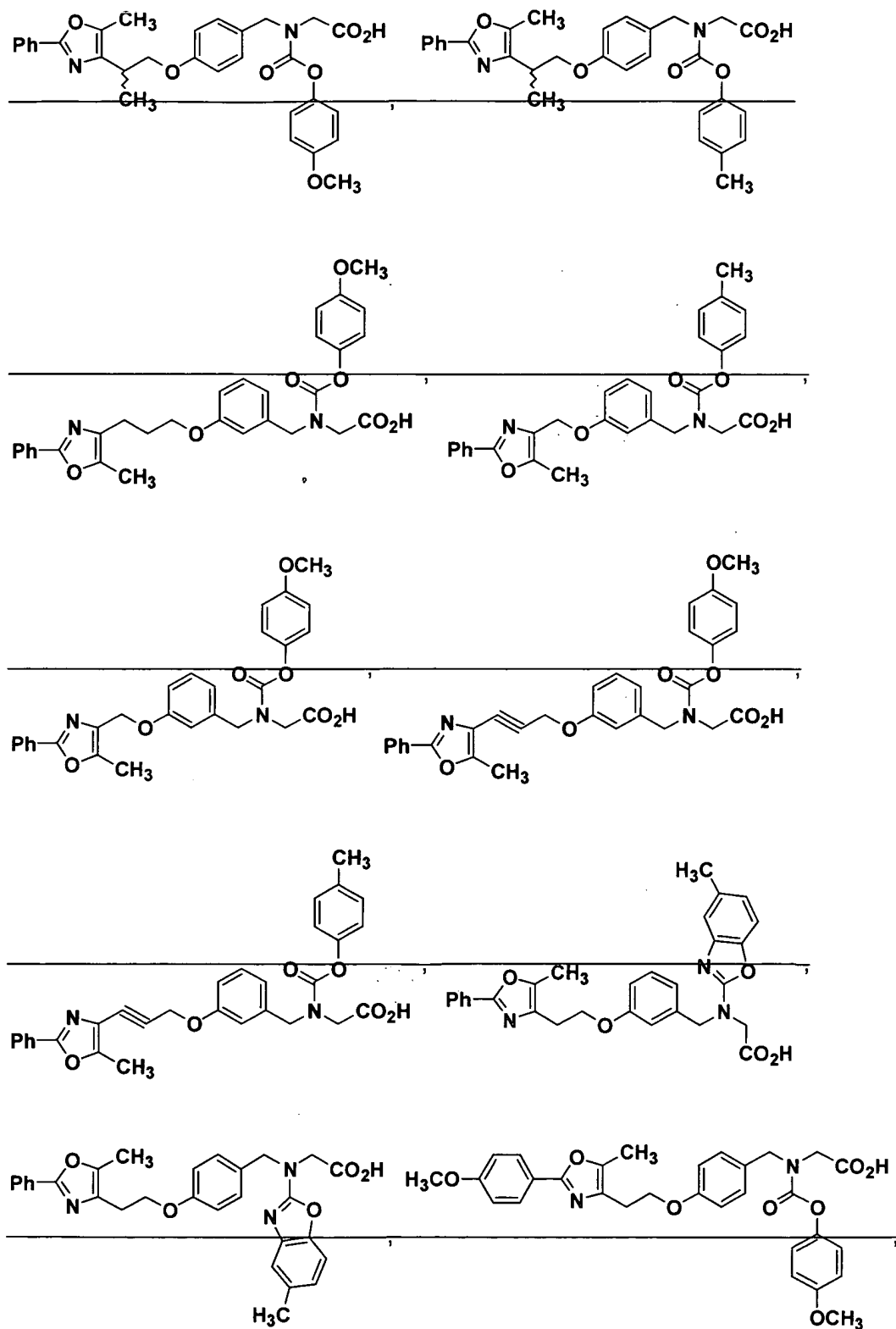


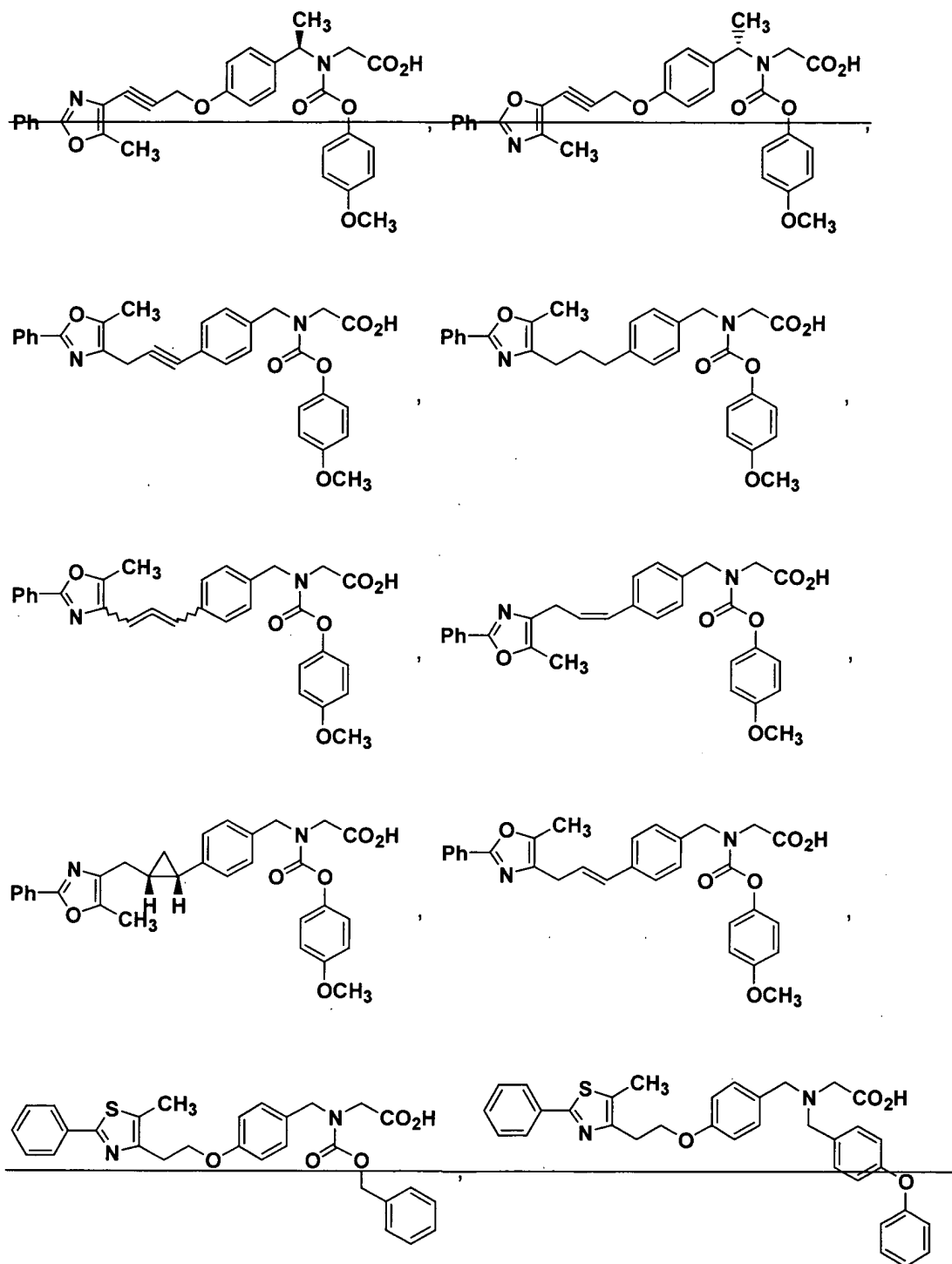


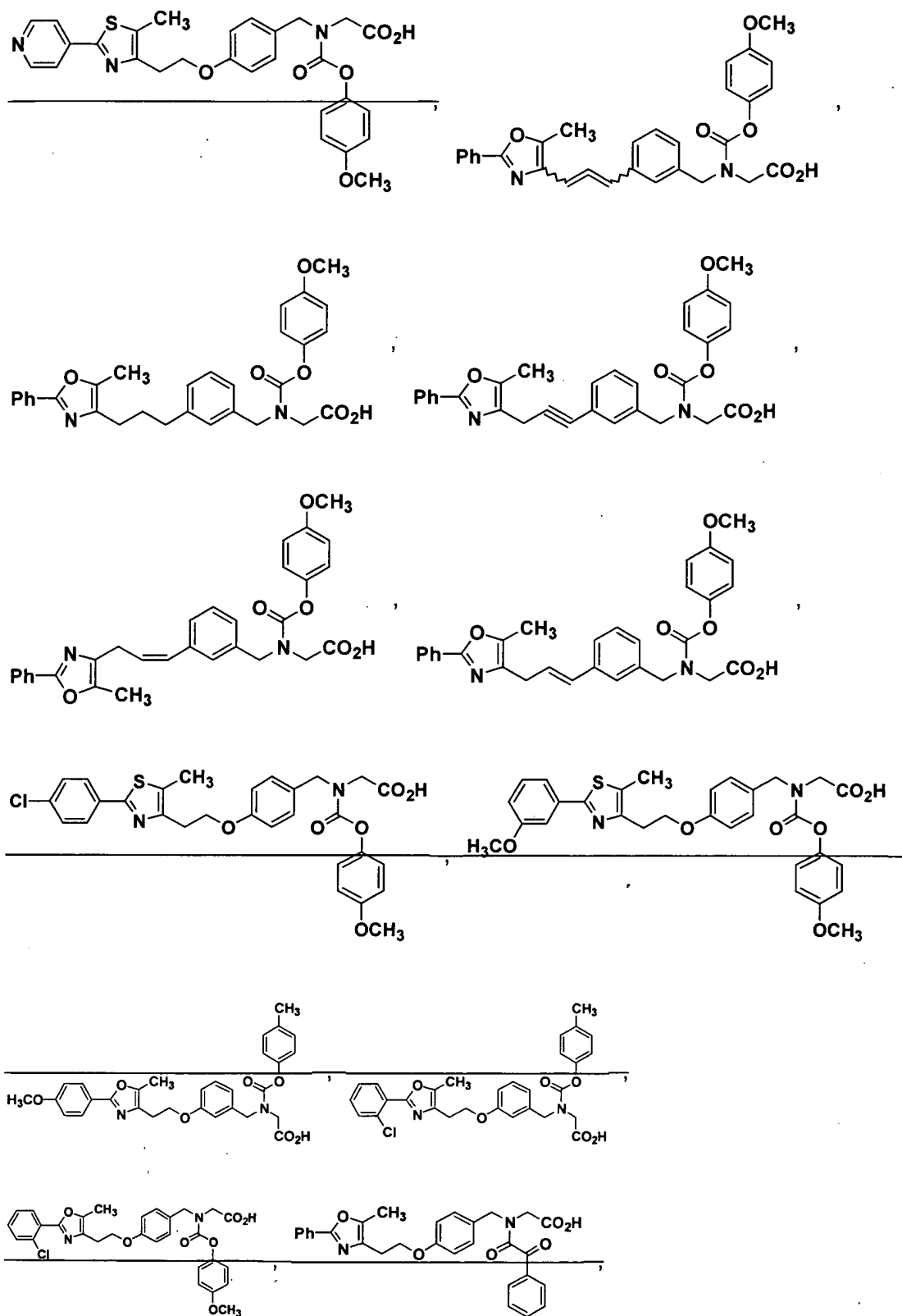


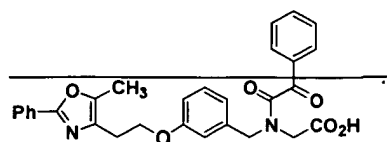






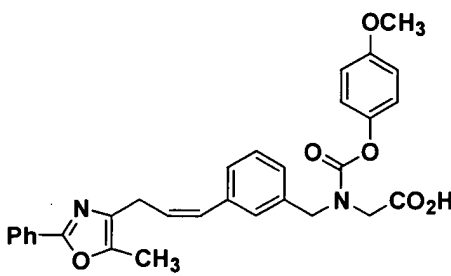
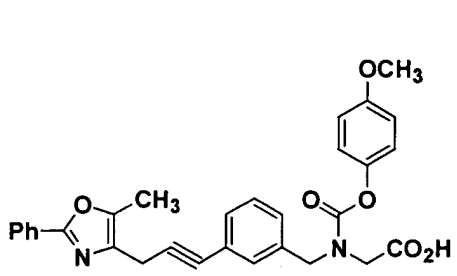
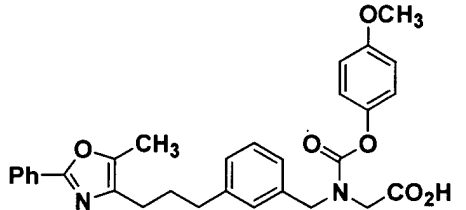
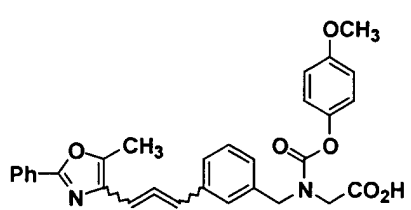
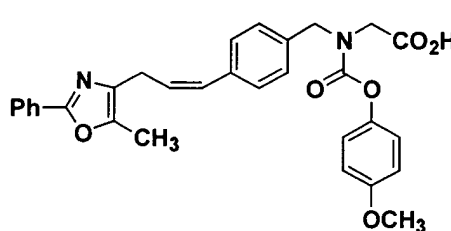
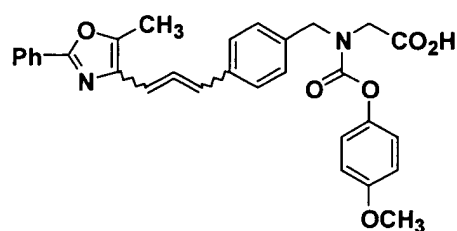
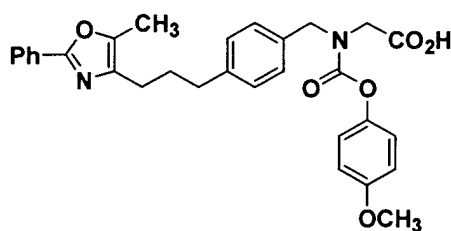
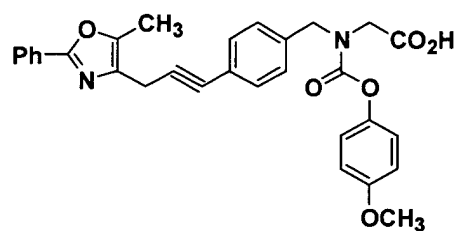


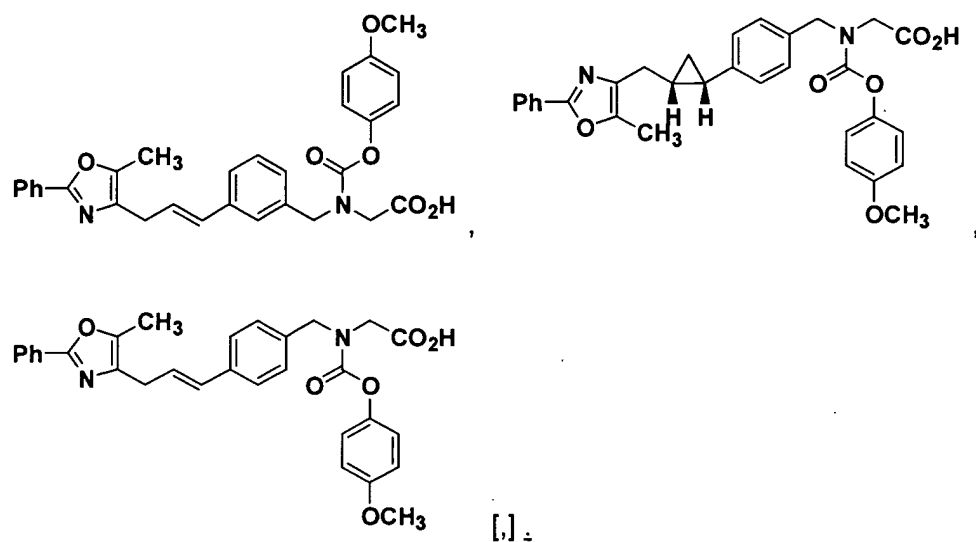




Claim 17. (Cancelled).

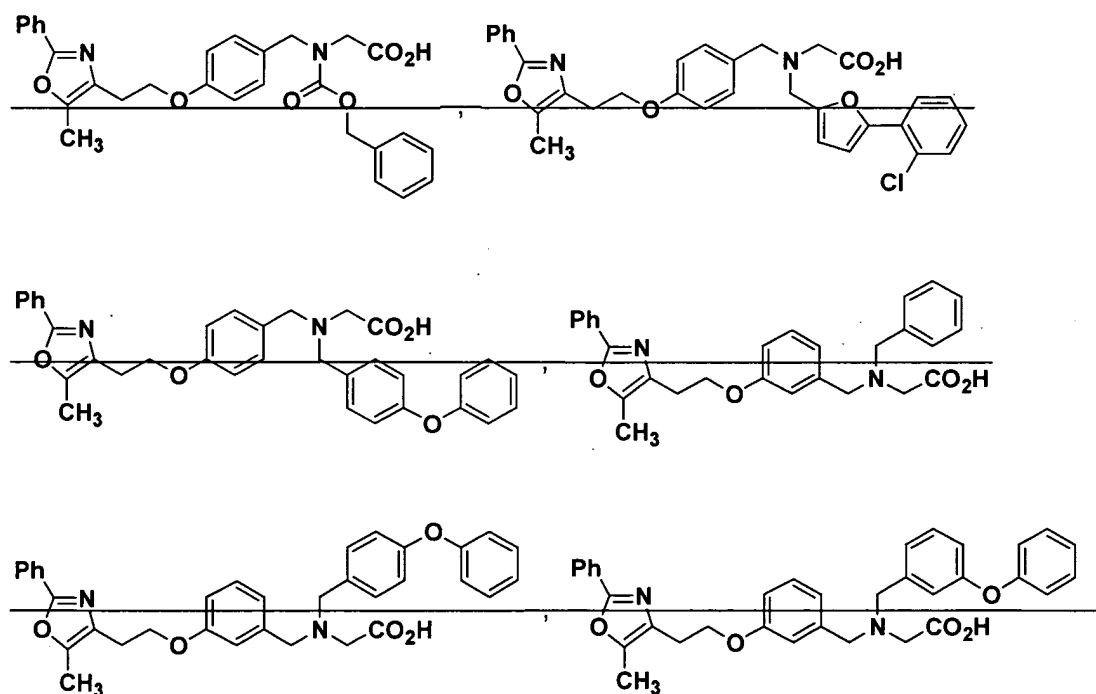
Claim 18. (Currently Amended) The ~~compound~~ method as defined in Claim 34 ~~1~~ having wherein the compound employed has the structure

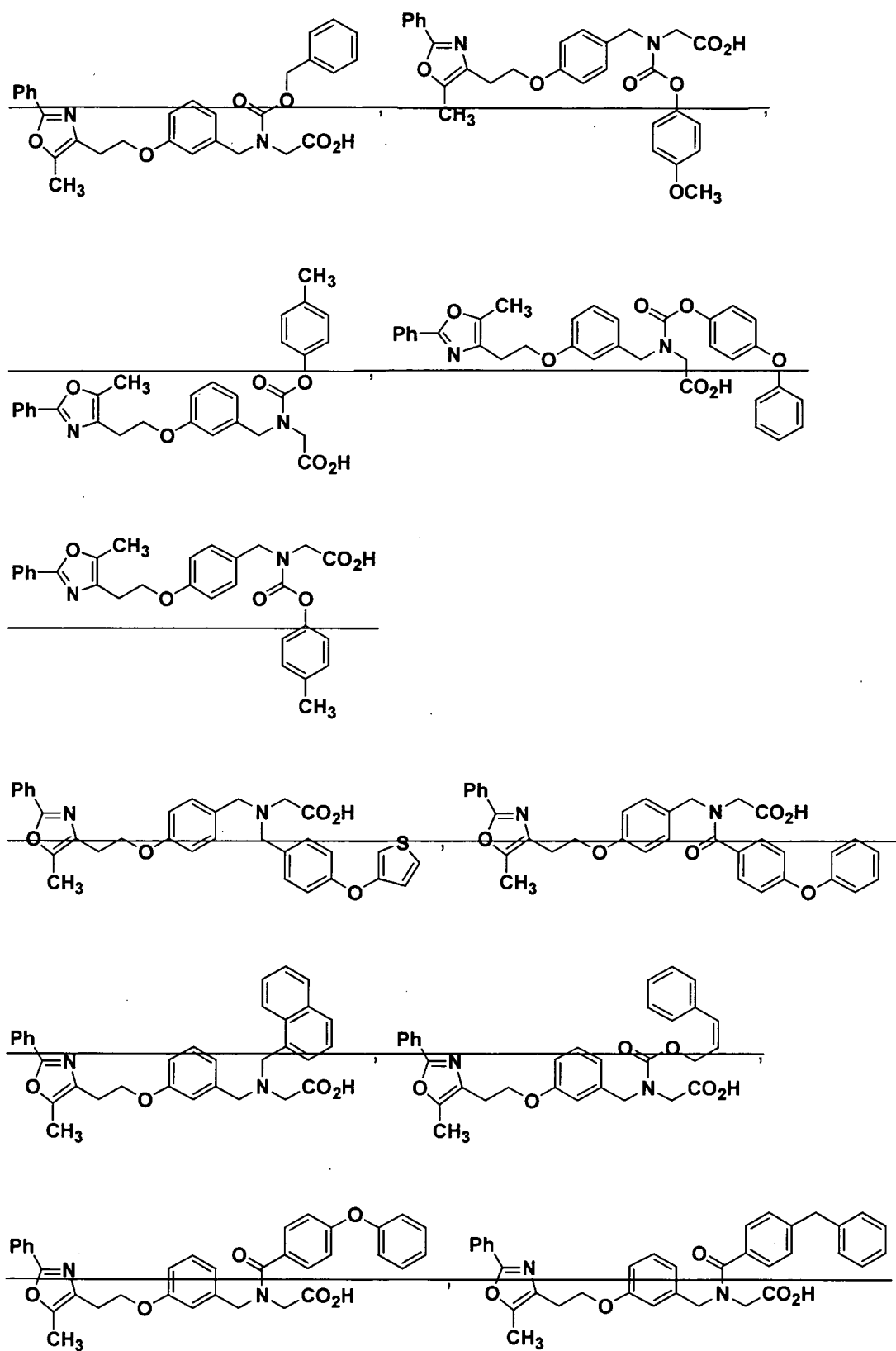


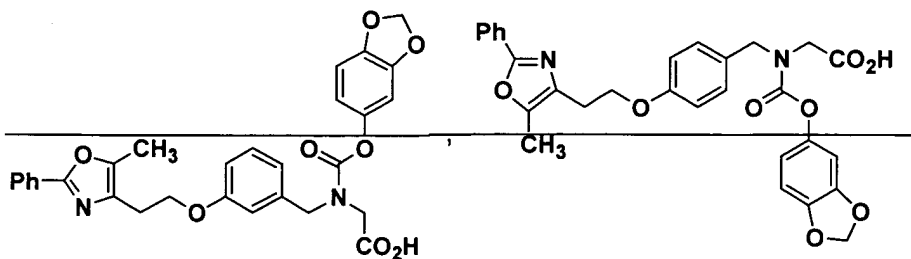
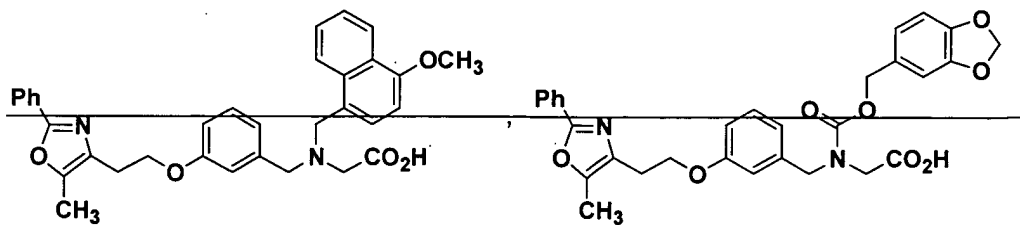
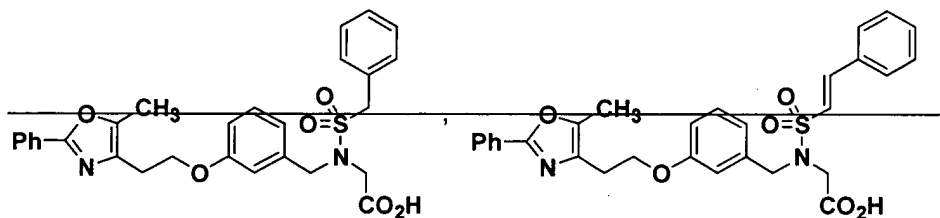
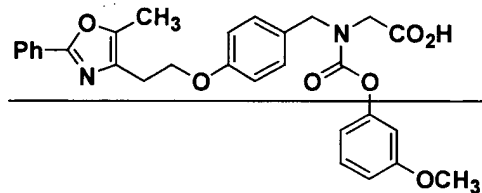
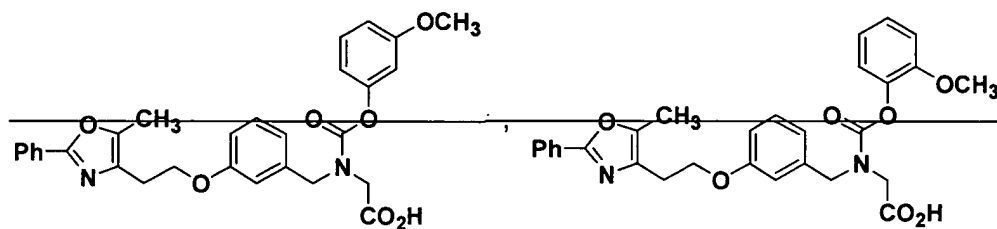
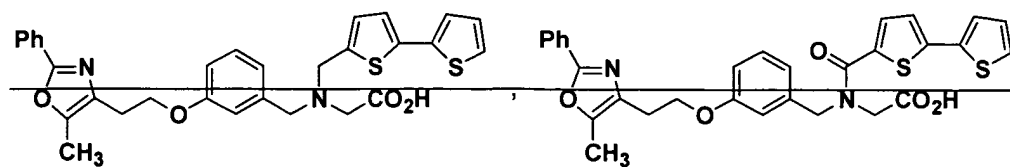


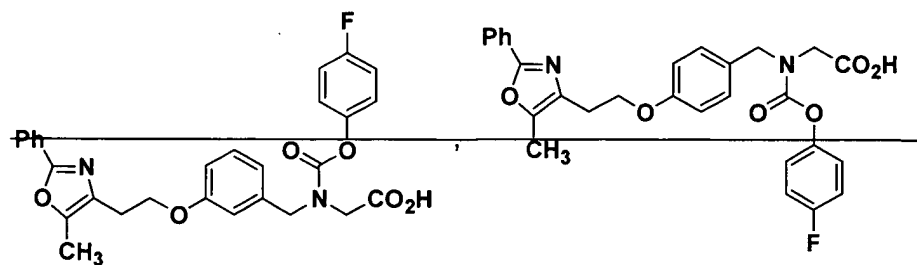
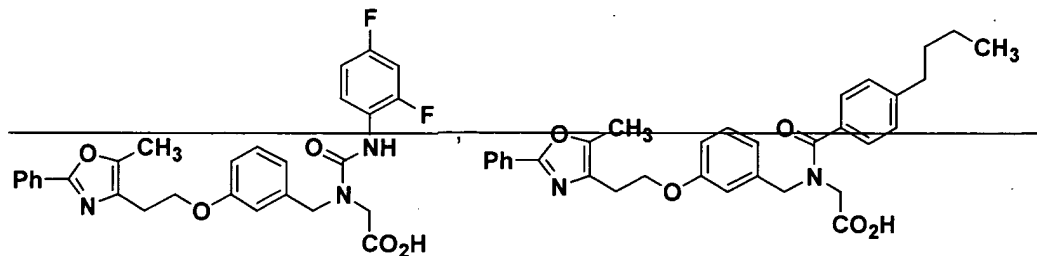
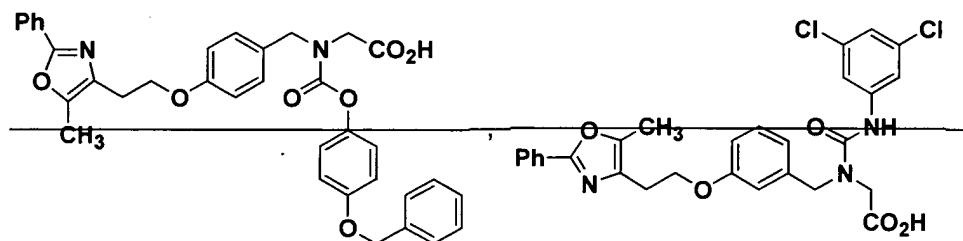
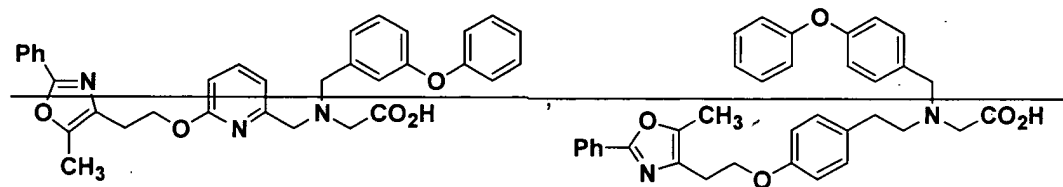
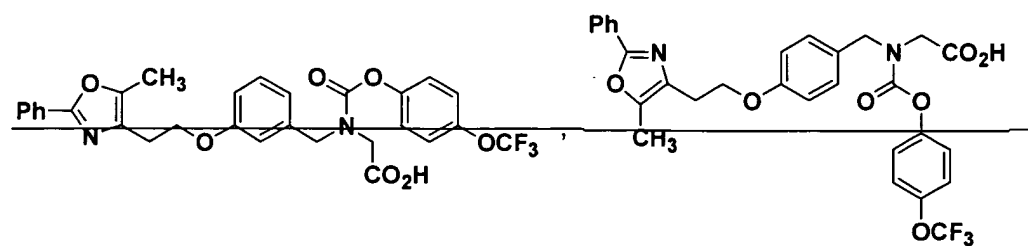
Claim 19. (Cancelled).

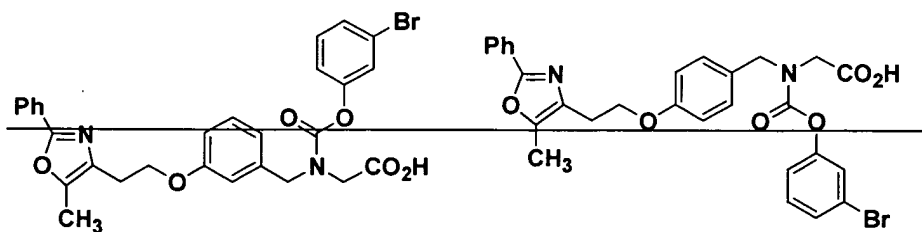
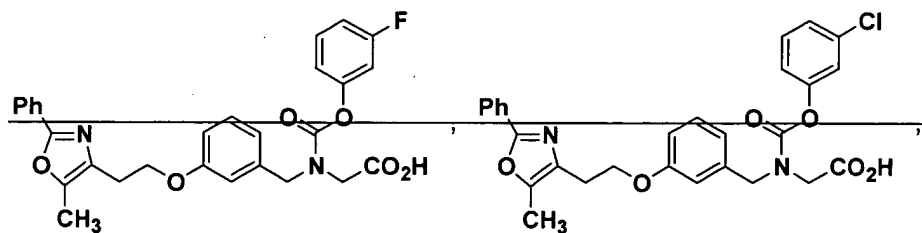
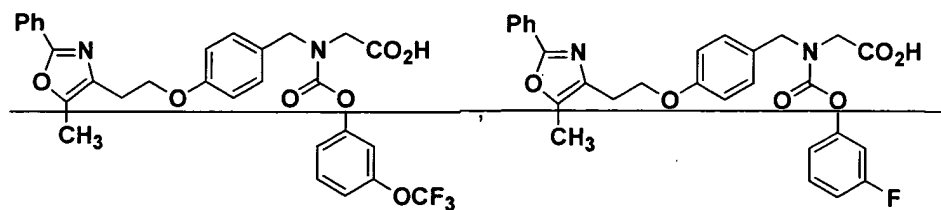
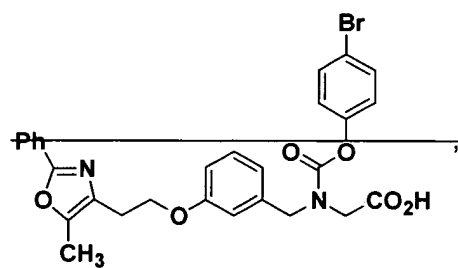
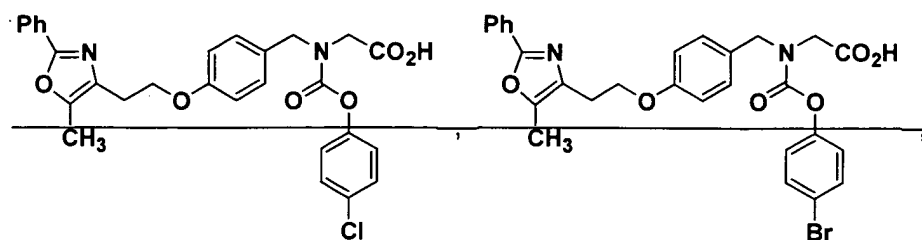
Claim 20. (Currently Amended) The ~~compound~~ method as defined in Claim 4 34 having wherein the compound employed has the structure

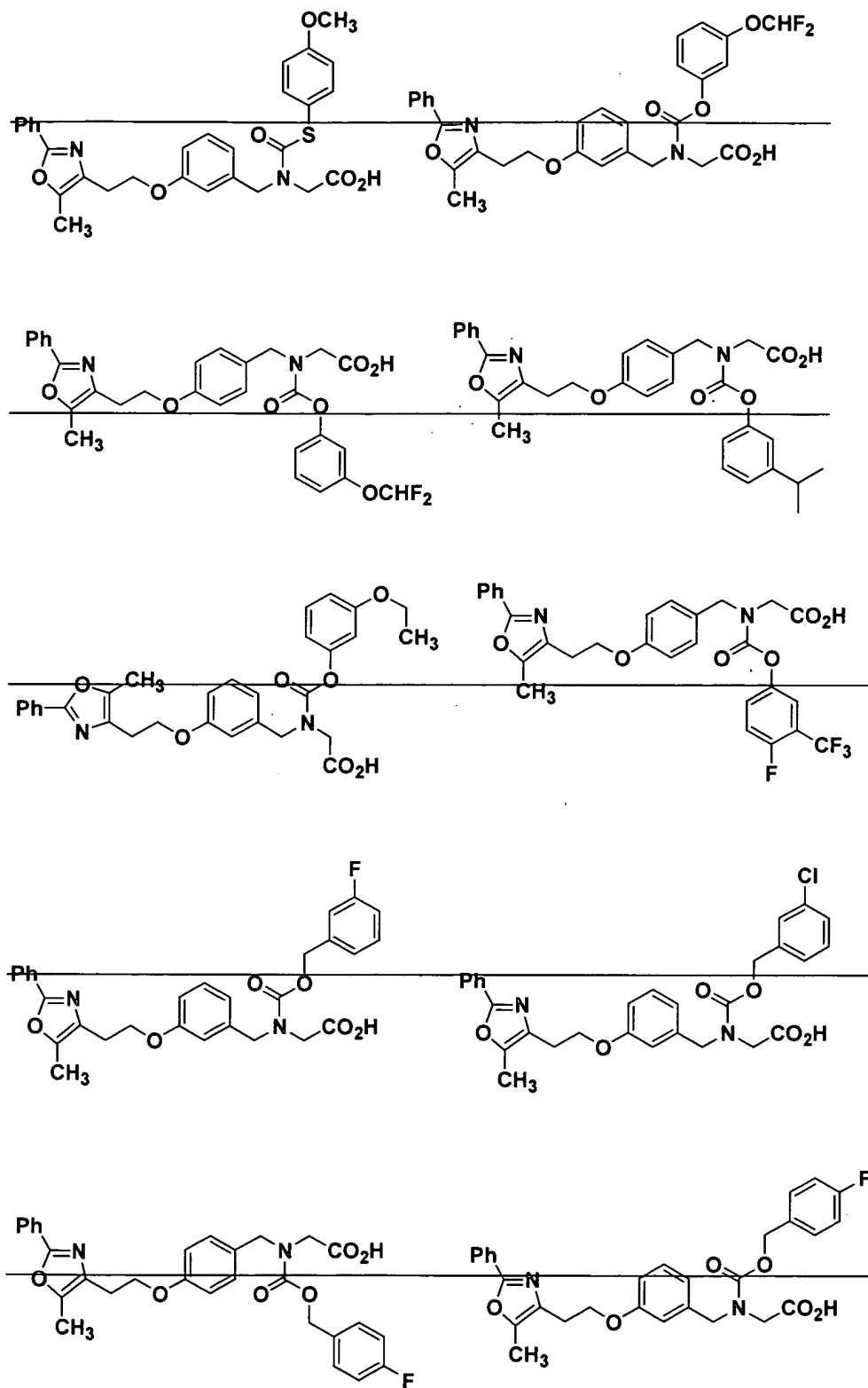


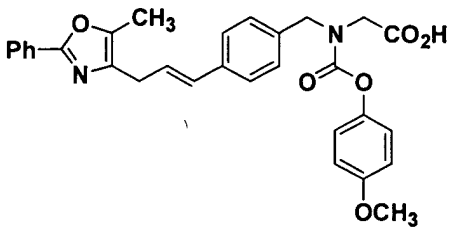
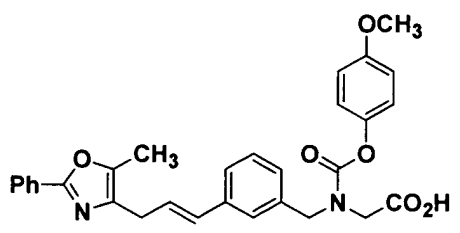
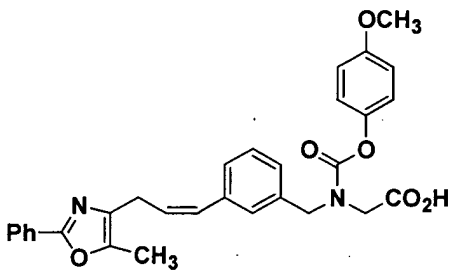
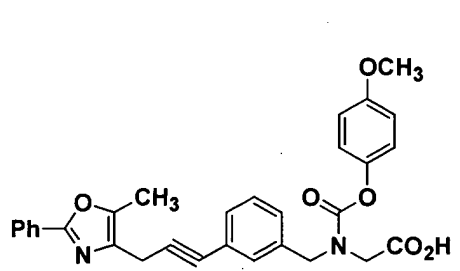
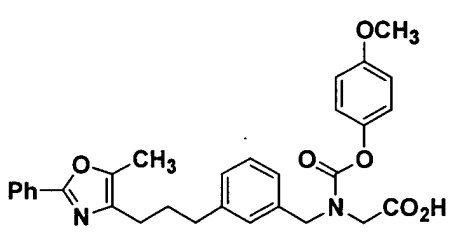
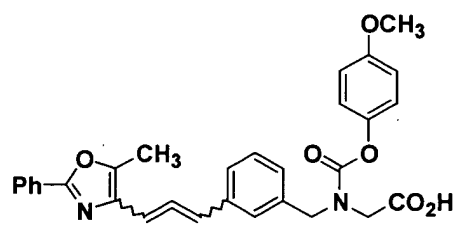
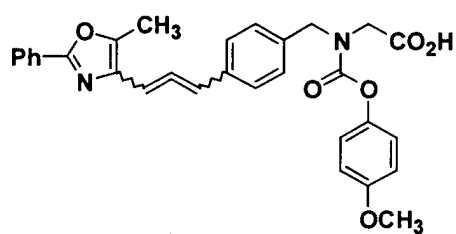
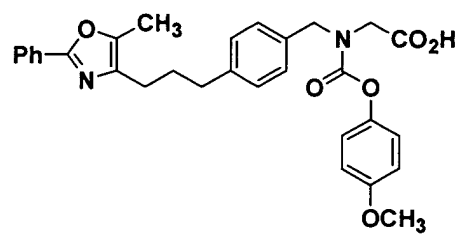
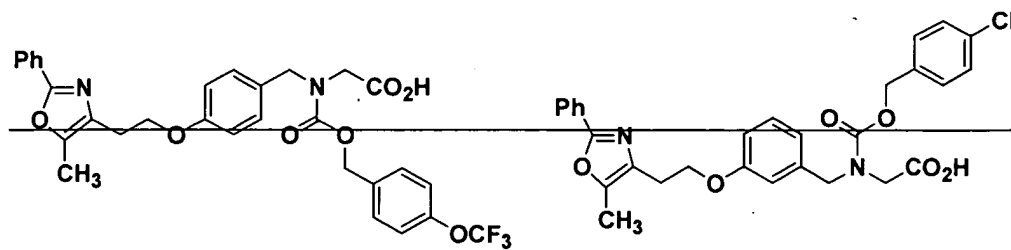


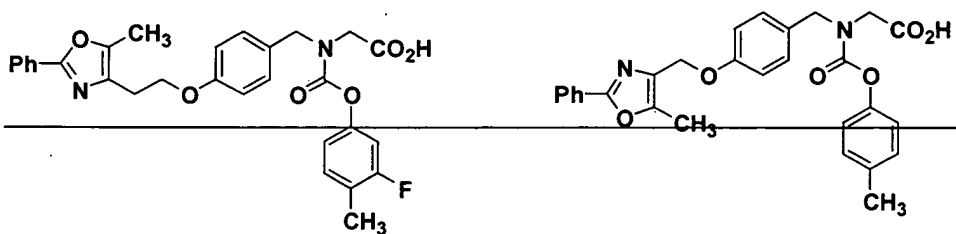
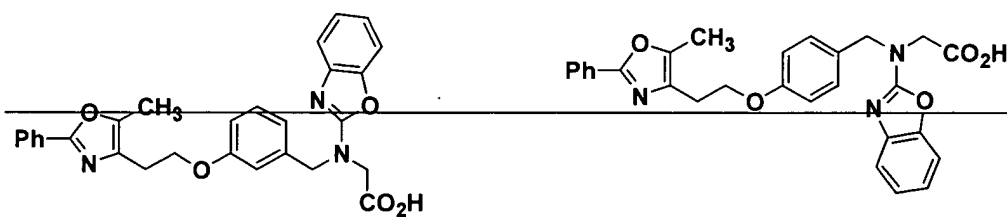
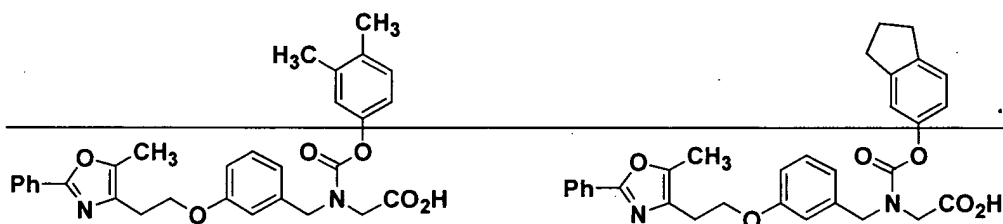
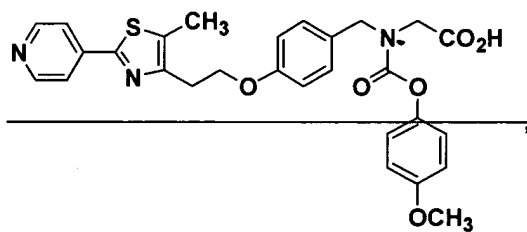
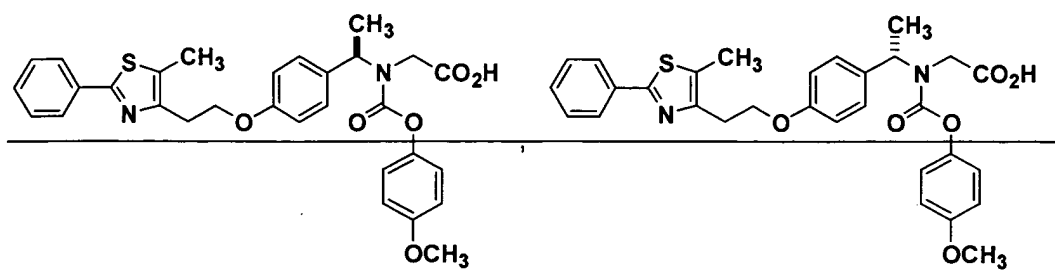


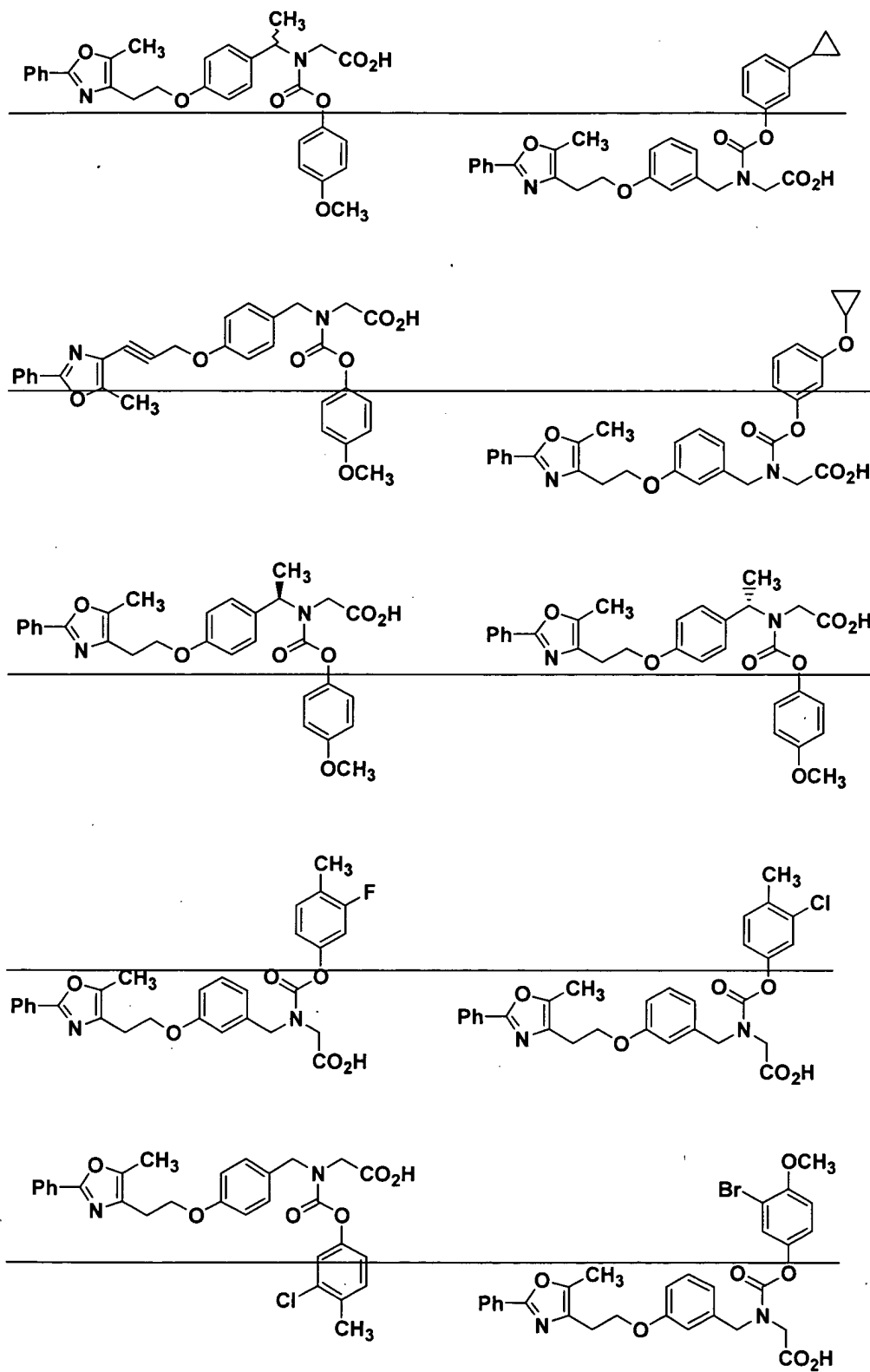


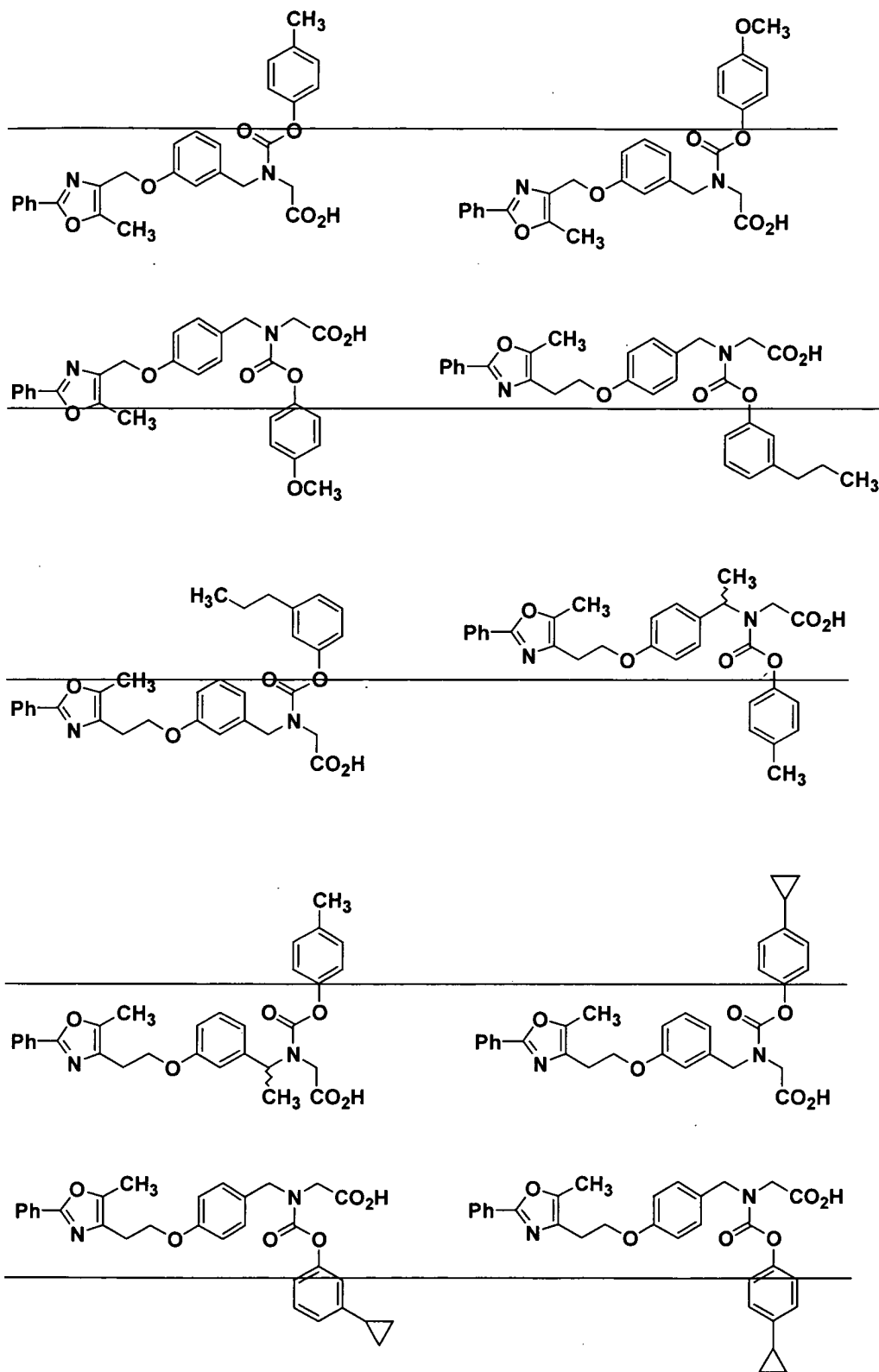


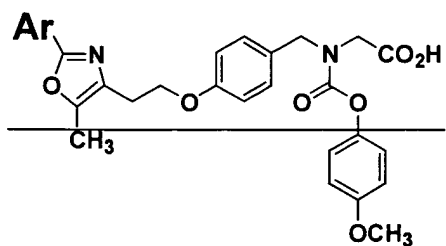
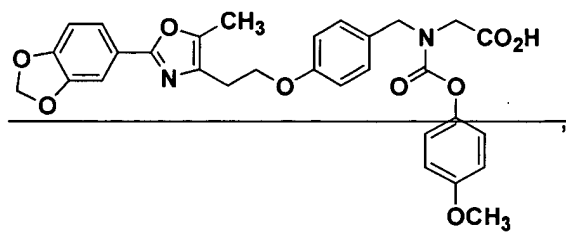
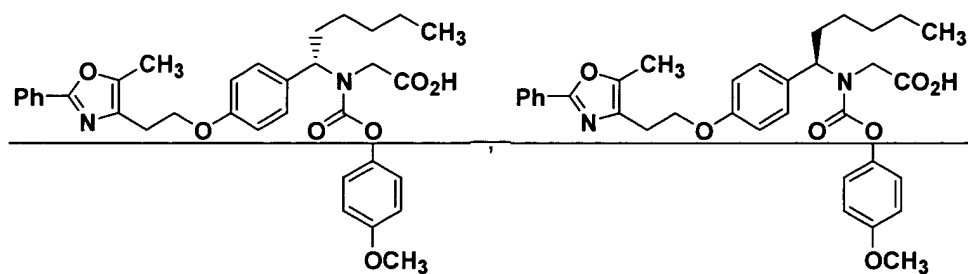
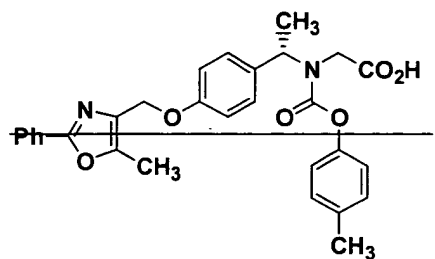
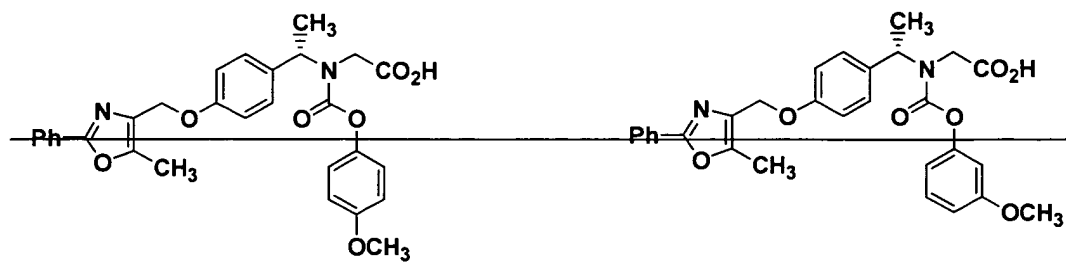


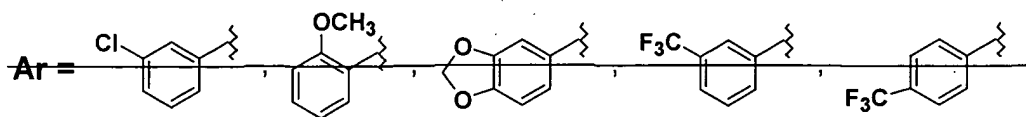
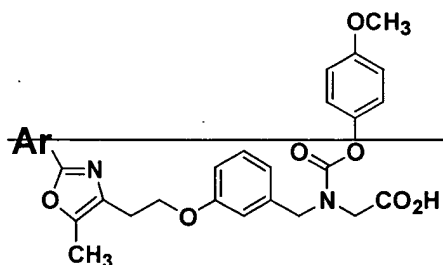
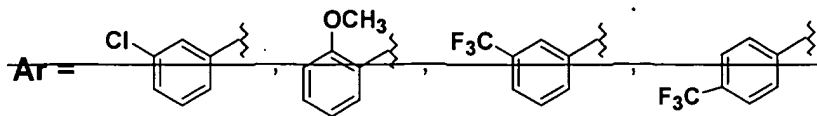






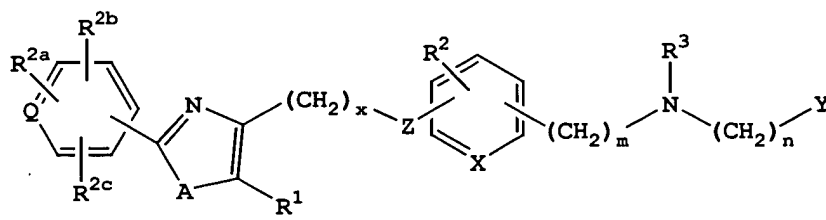






Claims 21 to 33. (Cancelled).

Claim 34. (Currently Amended) A method for lowering blood glucose levels or for treating diabetes, or for treating an early malignant disease, a malignant disease or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound ~~as defined in Claim 1~~ which has the structure



wherein x is 1, 2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R¹ is H or lower alkyl;

X is CH or N; with the proviso that where Z is O then Q is N or A is S or X is N;

R² is H, alkyl, alkoxy, halogen, amino or substituted amino;

R^{2a} , R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

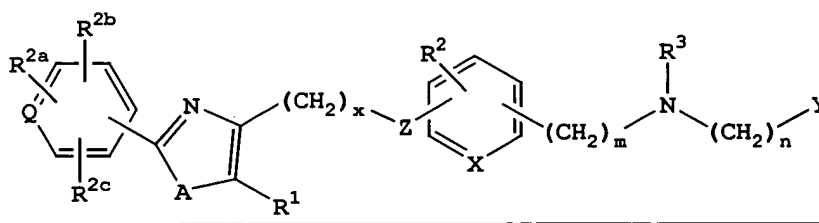
R^3 is aryloxycarbonyl, alkylloxycarbonyl, alkynylloxycarbonyl, alkenylloxycarbonyl, alkyl(halo)aryloxycarbonyl, alkyl(halo)aryloxycarbonyl cycloalkylaryloxycarbonyl, cycloalkylaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkylloxycarbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkylloxycarbonyl, alkylaryloxycarbonyl, alkynylloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxy carbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenylloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkylloxycarbonyl, aryloxyalkylloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylalkoxy carbonyl, heteroarylalkylloxyarylalkyl, arylalkenylarylalkyl, arylalkoxy carbonyl heteroarylalkyl, heteroaryloxyarylalkyl, arylalkenyl heteroarylalkyl or polyhaloalkylaryloxycarbonyl;

Y is CO_2R^4 where R^4 is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure $\text{P}(\text{O})(\text{OR}^{4a})\text{R}^5$ here R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl or a phosphonic acid of the structure $\text{P}(\text{O})(\text{OR}^{4a})_2$ where R^{4a} is H or a prodrug ester;

or stereoisomers thereof, a prodrug ester thereof, and a pharmaceutically acceptable salt thereof.

Claims 35 and 36. (Cancelled).

Claim 37. (Currently Amended) A pharmaceutical combination comprising a compound which has the structure



wherein x is 1, 2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R¹ is H or lower alkyl;

X is CH or N;

R² is H, alkyl, alkoxy, halogen, amino or substituted amino;

R^{2a}, R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R³ is aryloxy carbonyl, alkyl oxy carbonyl, alkynyl oxy carbonyl, alkenyl oxy carbonyl, alkyl(halo)aryloxy carbonyl, alkyl oxy(halo)aryloxy carbonyl, cycloalkyl aryloxy carbonyl, cycloalkyl oxy aryloxy carbonyl, alkyl carbonyl amino, aryl carbonyl amino, hetero aryl carbonyl amino, alkoxy carbonyl amino, aryloxy carbonyl amino, hetero aryl oxy carbonyl amino, alkyl sulfonyl, alkenyl sulfonyl, hetero aryl oxy carbonyl, cyclo hetero alkyl oxy carbonyl, hetero aryl alkenyl, hydroxy alkyl, alkoxy, alkoxy aryloxy carbonyl, aryl alkyl oxy carbonyl, alkyl aryloxy carbonyl, alkynyl oxy carbonyl, halo alkoxy aryloxy carbonyl, alkoxy carbonyl aryloxy carbonyl, aryloxy aryloxy carbonyl, aryl alkenyl oxy carbonyl, hetero aryl oxy aryl alkyl, aryloxy aryl alkyl oxy carbonyl, aryloxy alkyl oxy carbonyl, aryl alkyl sulfonyl, aryl thiocarbonyl, aryl alkenyl sulfonyl, hetero aryl sulfonyl, aryl sulfonyl, hetero aryl alkoxy carbonyl, hetero aryl alkyl oxy aryl alkyl, aryl alkenyl aryl alkyl, aryl alkoxy carbonyl hetero aryl alkyl, hetero aryl oxy aryl alkyl, aryl alkenyl hetero aryl alkyl or poly halo alkyl aryloxy carbonyl;

Y is CO₂R⁴ where R⁴ is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure P(O)(OR^{4a})R⁵ here R^{4a} is H or a prodrug ester, R⁵ is alkyl or aryl or a phosphonic acid of the structure P(O)(OR^{4a})₂ where R^{4a} is H or a prodrug ester;

or stereoisomers thereof, a prodrug ester thereof, or a pharmaceutically acceptable salt thereof as defined in Claim 1 and a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent which is other than a diuretic, a platelet aggregation inhibitor, and/or an antiosteoporosis agent.

Claim 38. (Cancelled)

Claim 39. (Currently Amended) The combination as defined in Claim 38 ~~37~~ wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR α agonist, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-I (GLP-I), insulin and/or a meglitinide; the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine)

reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent; the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor; the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β -adrenergic blocker.

40. (Currently Amended) The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipryride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A; the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol; the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427; the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S]([R*,R*])-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

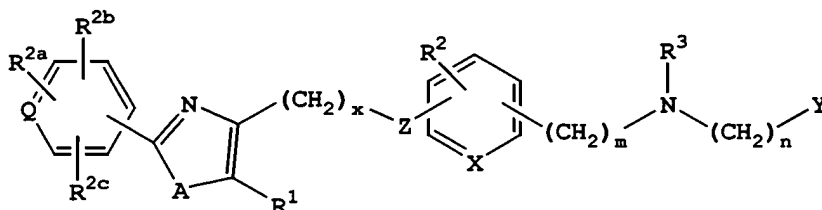
an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl; the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban.

Claims 41 to 49. (Cancelled).

Claim 50. (Currently Amended) A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia, or atherosclerosis, or for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis or osteoporosis, or psoriasis, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 43 37.

Claim 55. (New) A pharmaceutical combination comprising a compound which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R¹ is H or lower alkyl;

X is CH or N;

R² is H, alkyl, alkoxy, halogen, amino or substituted amino;

R^{2a}, R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R³ is aryloxy carbonyl, alkyl oxy carbonyl, alkynyl oxy carbonyl, alkenyl oxy carbonyl, alkyl(halo)aryloxy carbonyl, alkyl oxy(halo)aryloxy carbonyl, cycloalkyl aryloxy carbonyl, cycloalkyl oxy aryloxy carbonyl, alkyl carbonyl amino, aryl carbonyl amino, heteroaryl carbonyl amino, alkoxy carbonyl amino, aryloxy carbonyl amino, heteroaryl oxy carbonyl amino, alkyl sulfonyl, alkenyl sulfonyl, heteroaryl oxy carbonyl, cycloheteroalkyl oxy carbonyl, heteroaryl alkenyl, hydroxy alkyl, alkoxy, alkoxy aryloxy carbonyl, aryl alkyl oxy carbonyl, alkyl aryloxy carbonyl, alkynyl oxy carbonyl, haloalkoxy aryloxy carbonyl, alkoxy carbonyl aryloxy carbonyl, aryloxy aryloxy carbonyl, aryl alkenyl oxy carbonyl, heteroaryl oxy aryl alkyl, aryloxy aryl alkyl oxy carbonyl, aryloxy alkyl oxy carbonyl, aryl alkyl sulfonyl, aryl thiocarbonyl, aryl alkenyl sulfonyl, heteroaryl sulfonyl, aryl sulfonyl, heteroaryl alkoxy carbonyl, heteroaryl alkyl oxy aryl alkyl, aryl alkenyl aryl alkyl, aryl alkoxy carbonyl heteroaryl alkyl, heteroaryl oxy aryl alkyl, aryl alkenyl heteroaryl alkyl or polyhaloalkyl aryloxy carbonyl;

Y is CO₂R⁴ where R⁴ is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure P(O)(OR^{4a})R⁵ where R^{4a} is H or a prodrug ester, R⁵ is alkyl or aryl or a phosphonic acid of the structure P(O)(OR^{4a})₂ where R^{4a} is H or a prodrug ester;

or stereoisomers thereof, a prodrug ester thereof, or a pharmaceutically acceptable salt thereof, and an antihypertensive agent which is a diuretic.

Claim 56. (New) The combination as defined in Claim 55 wherein the diuretic is hydrochlorothiazide, torasemide, furosemide, spironolactone or indapamide.